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Form 1/77

Patents Act 1977

1 Title of invention

1 Please give the title of the invention

PURINE DERIVATIVES

2 Applicant's details

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2a If you are applying as a corporate body please give:

Corporate name
PFIZER LIMITED

Country *(and State of incorporation, if appropriate)*
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068926730 01

2b If you are applying as an individual or one of a partnership please give in full:

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K. S. RUDDOCK
Agent's address
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RAMSGATE ROAD
SANDWICH
KENT
Postcode CT13 9NJ

Agent's ADP number 06296446 001

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5 Claiming an earlier application dat

5 Are you claiming that this application be treated as having been filed on the date of filing of an earlier application?

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Yes ☐ No ☒ ➡ *go to 6*

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☐ number of earlier application or patent number

☐ filing date

(day month year)

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15(4) (Divisional) ☐ 8(3) ☐ 12(6) ☐ 37(4) ☐

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6

If you are declaring priority from a PCT Application please enter 'PCT' as the country and enter the country code (for example, GB) as part of the application number.

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7 Are you (the applicant or applicants) the sole inventor or the joint inventors?

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A statement of Inventorship on Patents Form 7/77 will need to be filed (see Rule 15).

8

Please supply duplicates of claim(s), abstract, description and drawing(s).

8 Checklist

8a Please fill in the number of sheets for each of the following types of document contained in this application.

Continuation sheets for this Patents Form 1/77			
Claim(s)		Description	69
Abstract		Drawing(s)	

8b Which of the following documents also accompanies the application?

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PURINE DERIVATIVES

This invention relates to purine derivatives. More particularly, this invention relates to 2-aminoalkyl-9-(tetrahydro-2-furanyl)-9H-purine derivatives and to processes for the preparation of, intermediates used in the preparation of, compositions containing and the uses of, such derivatives.

These derivatives are selective, functional agonists of the human adenosine A2a receptor and may be used as anti-inflammatory agents in the treatment of, *inter alia,* diseases of the respiratory tract.

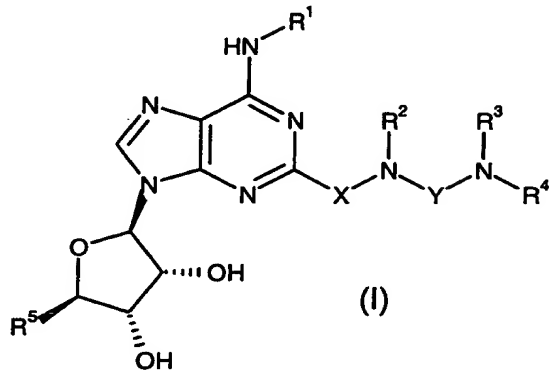
Adenosine is a ubiquitous molecule having a central role in mammalian intermediary metabolism. Independently, adenosine acts on multiple surface receptors to produce a variety of responses. Adenosine receptor classification has revealed the presence of at least four subtypes: A1, A2a, A2b and A3. Stimulation of adenosine A2 receptors on the surface of human neutrophils has been reported to potently inhibit a range of neutrophil functions. Activated neutrophils can damage lung tissue by release of reactive oxygen species, for example, superoxide anion radicals ($O_2^{\cdot-}$), and granule products, for example, human neutrophil elastase (HNE), amongst other inflammatory mediators. In addition, activated neutrophils perform both *de novo* synthesis and release of arachidonate products such as leukotriene B_4 (LTB_4). LTB_4 is a potent chemo-attractant that recruits additional neutrophils to the inflammatory focus, whereas released $O_2^{\cdot-}$ and HNE adversely affect the pulmonary extracellular matrix. The A2 receptor subtype mediating many of these responses ($O_2^{\cdot-}$ and LTB_4/HNE release and cell adhesion) is established as A2a. The A2 subtype (A2a or A2b) mediating the other effects remains to be established.

Selective agonist activity at the A2a receptor is considered to offer greater therapeutic benefit than the use of non-selective adenosine receptor agonists because interaction with other subtypes is associated with detrimental effects in the lung in animal models and human tissue studies. For example, asthmatics,

but not non-asthmatics, bronchoconstrict when challenged with inhaled adenosine. This response is at least in part due to the activation of the A1 receptor subtype. Activation of A1 receptors also promotes neutrophil chemotaxis and adherence to endothelial cells, thus promoting lung injury. Furthermore, many patients with respiratory disease will be co-prescribed β_2-agonists, and negative interaction has been shown in animal studies between isoprenaline and adenosine receptors negatively coupled to adenylate cyclase. Degranulation of human mast cells is promoted by activation of adenosine A2b receptors, thus selectivity over the A2b receptor is also advantageous.

We have now surprisingly found the present purine derivatives inhibit neutrophil function and are selective agonists of the adenosine A2a receptor. They may also have antagonist activity at the adenosine A3 receptor. The present compounds may be used to treat any disease for which an adenosine A2a receptor agonist is indicated. They can be used to treat a disease where leukocyte (e.g. neutrophil, eosinophil, basophil, lymphocyte, macrophage) - induced tissue damage is implicated. They are useful as anti-inflammatory agents in the treatment of diseases of the respiratory tract such as adult respiratory distress syndrome (ARDS), bronchitis, chronic bronchitis, chronic obstructive pulmonary disease, cystic fibrosis, asthma, emphysema, bronchiectasis, chronic sinusitis and rhinitis. The present compounds may also be used in the treatment of septic shock, male erectile dysfunction, hypertension, stroke, epilepsy, cerebral ischaemia, peripheral vascular disease, post-ischaemic reperfusion injury, diabetes, rheumatoid arthritis, multiple sclerosis, psoriasis, dermatitis, allergic dermatitis, eczema, ulcerative colitis, Crohns disease, inflammatory bowel disease, *Heliobacter pylori* gastritis, non-*Heliobacter pylori* gastritis, non-steroidal anti-inflammatory drug-induced damage to the gastro-intestinal tract or a psychotic disorder, or for wound healing.

Accordingly, the present invention provides a compound of the formula:



(I)

or a pharmaceutically acceptable salt or solvate thereof, wherein

R^1 is H, C_1-C_6 alkyl or fluorenyl, said C_1-C_6 alkyl being optionally substituted by 1 or 2 substituents each independently selected from phenyl and naphthyl, said phenyl and naphthyl being optionally substituted by C_1-C_6 alkyl, C_1-C_6 alkoxy, halo or cyano;

R^2 is H or C_1-C_6 alkyl;

either, R^3 and R^4, taken together with the nitrogen atom to which they are attached, represent azetidinyl, pyrrolidinyl, piperidinyl, piperazinyl, homopiperidinyl or homopiperazinyl, each being optionally substituted on a ring nitrogen or carbon atom by C_1-C_6 alkyl or C_3-C_8 cycloalkyl and optionally substituted on a ring carbon atom not adjacent to a ring nitrogen atom by $-NR^6R^7$,

or, R^3 is H, C_1-C_6 alkyl, C_3-C_8 cycloalkyl or benzyl and R^4 is

(a) azetidin-3-yl, pyrrolidin-3-yl, piperidin-3-yl, piperidin-4-yl, homopiperidin-3-yl or homopiperidin-4-yl, each being optionally substituted by C_1-C_6 alkyl, C_3-C_8 cycloalkyl or benzyl, or

(b) -(C_2-C_6 alkylene)-R^8, or

(c) -(C_1-C_6 alkylene)-R^{13};

R^5 is CH_2OH or $CONR^{14}R^{14}$;

R^6 and R^7 are either each independently H or C_1-C_6 alkyl or, taken together with the nitrogen atom to which they are attached, represent azetidinyl, pyrrolidinyl or piperidinyl, said azetidinyl, pyrrolidinyl and piperidinyl being optionally substituted by C_1-C_6 alkyl;

R^8 is (i) azetidin-1-yl, pyrrolidin-1-yl, piperidin-1-yl, morpholin-4-yl, piperazin-1-yl, homopiperidin-1-yl, homopiperazin-1-yl or tetrahydroisoquinolin-1-yl, each being optionally substituted on a ring carbon atom by C_1-C_6 alkyl, C_3-C_8 cycloalkyl, phenyl, C_1-C_6 alkoxy-(C_1-C_6)-alkyl, R^9R^9N-(C_1-C_6)-alkyl, fluoro-(C_1-C_6)-alkyl, $-CONR^9R^9$, $-COOR^9$ or C_2-C_5 alkanoyl, and optionally substituted on a ring carbon atom not adjacent to a ring nitrogen atom by fluoro-(C_1-C_6)-alkoxy, halo, $-OR^9$, cyano, $-S(O)_mR^{10}$, $-NR^9R^9$, $-SO_2NR^9R^9$, $-NR^9COR^{10}$ or $-NR^9SO_2R^{10}$, and said piperazin-1-yl and homopiperazin-1-yl being optionally substituted on the ring nitrogen atom not attached to the C_2-C_6 alkylene group by C_1-C_6 alkyl, phenyl, C_1-C_6 alkoxy-(C_2-C_6)-alkyl, R^9R^9N-(C_2-C_6)-alkyl, fluoro-(C_1-C_6)-alkyl, C_2-C_5 alkanoyl, $-COOR^{10}$, C_3-C_8 cycloalkyl, $-SO_2R^{10}$, $-SO_2NR^9R^9$ or $-CONR^9R^9$, or

(ii) $NR^{11}R^{12}$;

R^9 is H, C_1-C_6 alkyl, C_3-C_8 cycloalkyl or phenyl;

R^{10} is C_1-C_6 alkyl, C_3-C_8 cycloalkyl or phenyl;

R^{11} is H, C_1-C_6 alkyl, C_3-C_8 cycloalkyl or benzyl;

R^{12} is H, C_1-C_6 alkyl, C_3-C_8 cycloalkyl, phenyl, benzyl, fluoro-(C_1-C_6)-alkyl, $-CONR^9R^9$, $-COOR^{10}$, C_2-C_5 alkanoyl or $-SO_2NR^9R^9$;

R^{13} is phenyl, pyridin-2-yl, pyridin-3-yl or pyridin-4-yl, each being optionally substituted by C_1-C_6 alkyl, C_1-C_6 alkoxy, halo or cyano;

R^{14} is H or C_1-C_6 alkyl optionally substituted by cyclopropyl;

m is 0, 1 or 2;

X is $-CH_2-$ or $-CH_2CH_2-$; and

Y is CO, CS, SO_2 or C=N(CN).

In the above definitions, halo means fluoro, chloro, bromo or iodo and alkyl, alkylene, alkanoyl and alkoxy groups containing the requisite number of carbon atoms can be unbranched or branched chain. Examples of alkyl include methyl, ethyl, n-propyl, i-propyl, n-butyl, i-butyl, sec-butyl and t-butyl. Examples of alkoxy include methoxy, ethoxy, n-propoxy, i-propoxy, n-butoxy, i-butoxy, sec-butoxy and t-butoxy. Examples of alkanoyl include acetyl and propanoyl. Examples of alkylene include methylene, 1,1-ethylene, 1,2-ethylene, 1,1-propylene, 1,2-propylene, 1,3-propylene and 2,2-propylene. Examples of cycloalkyl include cyclopropyl, cyclobutyl, cyclopentyl, cyclohexyl and cycloheptyl.

The pharmaceutically acceptable salts of the compounds of the formula (I) include the acid addition and the base salts thereof.

Suitable acid addition salts are formed from acids which form non-toxic salts and examples are the hydrochloride, hydrobromide, hydroiodide, sulphate, bisulphate, nitrate, phosphate, hydrogen phosphate, acetate, maleate, fumarate, lactate, tartrate, citrate, gluconate, succinate, saccharate, benzoate, methanesulphonate, ethanesulphonate, benzenesulphonate, para-toluenesulphonate and pamoate salts.

Suitable base salts are formed from bases which form non-toxic salts and examples are the sodium, potassium, aluminium, calcium, magnesium, zinc and diethanolamine salts.

For a review on suitable salts see Berge *et al*, *J. Pharm. Sci.*, **66**, 1-19, 1977.

The pharmaceutically acceptable solvates of the compounds of the formula (I) include the hydrates thereof.

Also included within the present scope of the compounds of the formula (I) are polymorphs thereof.

A compound of the formula (I) may contain one or more additional asymmetric carbon atoms and therefore exist in two or more stereoisomeric forms. The present invention includes the individual stereoisomers of the compounds of the formula (I) together with mixtures thereof.

Separation of diastereoisomers may be achieved by conventional techniques, e.g. by fractional crystallisation, chromatography or H.P.L.C. of a stereoisomeric mixture of a compound of the formula (I) or a suitable salt or derivative thereof. An individual enantiomer of a compound of the formula (I) may also be prepared from a corresponding optically pure intermediate or by resolution, such as by H.P.L.C. of the corresponding racemate using a suitable chiral support or by fractional crystallisation of the diastereoisomeric salts formed by reaction of the corresponding racemate with a suitable optically active acid or base, as appropriate.

Preferably, R^1 is C_1-C_6 alkyl optionally substituted by 1 or 2 phenyl substituents, said phenyl being optionally substituted by halo.
Preferably, R^1 is C_1-C_6 alkyl substituted by 1 or 2 phenyl substituents, said phenyl being optionally substituted by halo.
Preferably, R^1 is C_1-C_4 alkyl substituted by 1 or 2 phenyl substituents, said phenyl being optionally substituted by halo.
Preferably, R^1 is C_1-C_2 alkyl substituted by 1 or 2 phenyl substituents, said phenyl being optionally substituted by halo.

Preferably, R^1 is ethyl substituted by 1 or 2 phenyl substituents, said phenyl being optionally substituted by halo.
Preferably, R^1 is diphenylethyl or [di(chlorophenyl)]ethyl.
Preferably, R^1 is 2,2-diphenylethyl or 2,2-[di(4-chlorophenyl)]ethyl.

Preferably, R^2 is H.

Preferably, R^3 is H.

Preferably, R^4 is -(C_2-C_6 alkylene)-R^8 or piperidin-4-yl optionally substituted by benzyl.
Preferably, R^4 is -(C_2-C_4 alkylene)-R^8 or piperidin-4-yl substituted by benzyl.
Preferably, R^4 is -CH_2CH_2-R^8 or 1-benzylpiperidin-4-yl.

Preferably, R^5 is CH_2OH or CONH(C_1-C_6 alkyl).
Preferably, R^5 is CH_2OH or CONH(C_1-C_4 alkyl).
Preferably, R^5 is CH_2OH or CONH(C_1-C_2 alkyl).
Preferably, R^5 is CH_2OH or $CONHCH_2CH_3$.

Preferably, R^8 is piperidin-1-yl optionally substituted on a ring carbon by C_1-C_6 alkyl or $NR^{11}R^{12}$.
Preferably, R^8 is piperidin-1-yl optionally substituted on a ring carbon by C_1-C_4 alkyl or $NR^{11}R^{12}$.
Preferably, R^8 is piperidin-1-yl optionally substituted on a ring carbon by C_1-C_2 alkyl or $NR^{11}R^{12}$.
Preferably, R^8 is piperidin-1-yl optionally substituted on a ring carbon by methyl or $NR^{11}R^{12}$.
Preferably, R^8 is piperidin-1-yl, 2,2,6,6-tetramethylpiperidin-1-yl or $NR^{11}R^{12}$.

Preferably, R^{11} is C_1-C_6 alkyl or C_3-C_8 cycloalkyl.
Preferably, R^{11} is C_1-C_4 alkyl or C_3-C_6 cycloalkyl.
Preferably, R^{11} is propyl, butyl, cyclobutyl or cyclopentyl.

Preferably, R^{11} is prop-2-yl, but-1-yl, cyclobutyl or cyclopentyl.

Preferably, R^{12} is C_1-C_6 alkyl or C_3-C_8 cycloalkyl.

Preferably, R^{12} is C_1-C_4 alkyl or C_3-C_6 cycloalkyl.

Preferably, R^{12} is propyl, butyl, cyclobutyl or cyclopentyl.

Preferably, R^{12} is prop-2-yl, but-1-yl, cyclobutyl or cyclopentyl.

Preferably, X is $-CH_2-$.

Preferably, Y is CO or C=N(CN).

Preferably, Y is CO.

Preferred examples of a compound of the formula (I) include:

N-({9-[(2*R*,3*R*,4*S*,5*R*)-3,4-dihydroxy-5-(hydroxymethyl)tetrahydro-2-furanyl]-6-[(2,2-diphenylethyl)amino]-9*H*-purin-2-yl}methyl)-*N*'-[2-(diisopropylamino)ethyl]urea;

N-({9-[(2*R*,3*R*,4*S*,5*R*)-3,4-dihydroxy-5-(hydroxymethyl)tetrahydro-2-furanyl]-6-[(2,2-diphenylethyl)amino]-9*H*-purin-2-yl}methyl)-*N*'-[2-(1-piperidinyl)ethyl]urea;

(2*S*,3*S*,4*R*,5*R*)-5-{2-{[({[2-(diisopropylamino)ethyl]amino}carbonyl)amino]methyl}-6-[(2,2-diphenylethyl)amino]-9*H*-purin-9-yl}-*N*-ethyl-3,4-dihydroxytetrahydro-2-furancarboxamide;

(2*S*,3*S*,4*R*,5*R*)-5-(6-[(2,2-diphenylethyl)amino]-2-{[({[2-(1-piperidinyl)ethyl]amino}carbonyl)amino]methyl}-9*H*-purin-9-yl)-*N*-ethyl-3,4-dihydroxytetrahydro-2-furancarboxamide;

N-({6-{[2,2-bis(4-chlorophenyl)ethyl]amino}-9-[(2*R*,3*R*,4*S*,5*R*)-3,4-dihydroxy-5-(hydroxymethyl)tetrahydro-2-furanyl]-9*H*-purin-2-yl}methyl)-*N*'-[2-(diisopropylamino)ethyl]urea;

N-[2-(dicyclobutylamino)ethyl]-*N*'-({9-[(2*R*,3*R*,4*S*,5*R*)-3,4-dihydroxy-5-(hydroxymethyl)tetrahydro-2-furanyl]-6-[(2,2-diphenylethyl)amino]-9*H*-purin-2-yl}methyl)urea;

N-[2-(di-n-butylamino)ethyl]-*N'*-({9-[(2*R*,3*R*,4*S*,5*R*)-3,4-dihydroxy-5-(hydroxymethyl)tetrahydro-2-furanyl]-6-[(2,2-diphenylethyl)amino]-9*H*-purin-2-yl}methyl)urea;

(2*S*,3*S*,4*R*,5*R*)-5-{2-{[((*E*)-(cyanoimino){[2-(1-piperidinyl)ethyl]amino}methyl)amino]methyl}-6-[(2,2-diphenylethyl)amino]-9*H*-purin-9-yl}-*N*-ethyl-3,4-dihydroxytetrahydro-2-furancarboxamide;

(2*S*,3*S*,4*R*,5*R*)-5-{2-[({[(1-benzyl-4-piperidinyl)amino]carbonyl}amino)methyl]-6-[(2,2-diphenylethyl)amino]-9*H*-purin-9-yl}-*N*-ethyl-3,4-dihydroxytetrahydro-2-furancarboxamide;

(2*S*,3*S*,4*R*,5*R*)-5-{2-({[({2-[cyclopentyl(isopropyl)amino]ethyl}amino)carbonyl]amino}methyl)-6-[(2,2-diphenylethyl)amino]-9*H*-purin-9-yl}-*N*-ethyl-3,4-dihydroxytetrahydro-2-furancarboxamide;

(2*S*,3*S*,4*R*,5*R*)-5-{2-{[({[2-(di-n-butylamino)ethyl]amino}carbonyl)amino]methyl}-6-[(2,2-diphenylethyl)amino]-9*H*-purin-9-yl}-*N*-ethyl-3,4-dihydroxytetrahydro-2-furancarboxamide;

(2*S*,3*S*,4*R*,5*R*)-5-(6-{[2,2-bis(4-chlorophenyl)ethyl]amino}-2-{[({[2-(diisopropylamino)ethyl]amino}carbonyl)amino]methyl}-9*H*-purin-9-yl)-*N*-ethyl-3,4-dihydroxytetrahydro-2-furancarboxamide;

N-({9-[(2*R*,3*R*,4*S*,5*R*)-3,4-dihydroxy-5-(hydroxymethyl)tetrahydro-2-furanyl]-6-[(2,2-diphenylethyl)amino]-9*H*-purin-2-yl}methyl)-*N'*-[2-(2,2,6,6-tetramethyl-1-piperidinyl)ethyl]urea; and

(2*S*,3*S*,4*R*,5*R*)-5-(6-[(2,2-diphenylethyl)amino]-2-{[({[2-(2,2,6,6-tetramethyl-1-piperidinyl)ethyl]amino}carbonyl)amino]methyl}-9*H*-purin-9-yl)-*N*-ethyl-3,4-dihydroxytetrahydro-2-furancarboxamide;

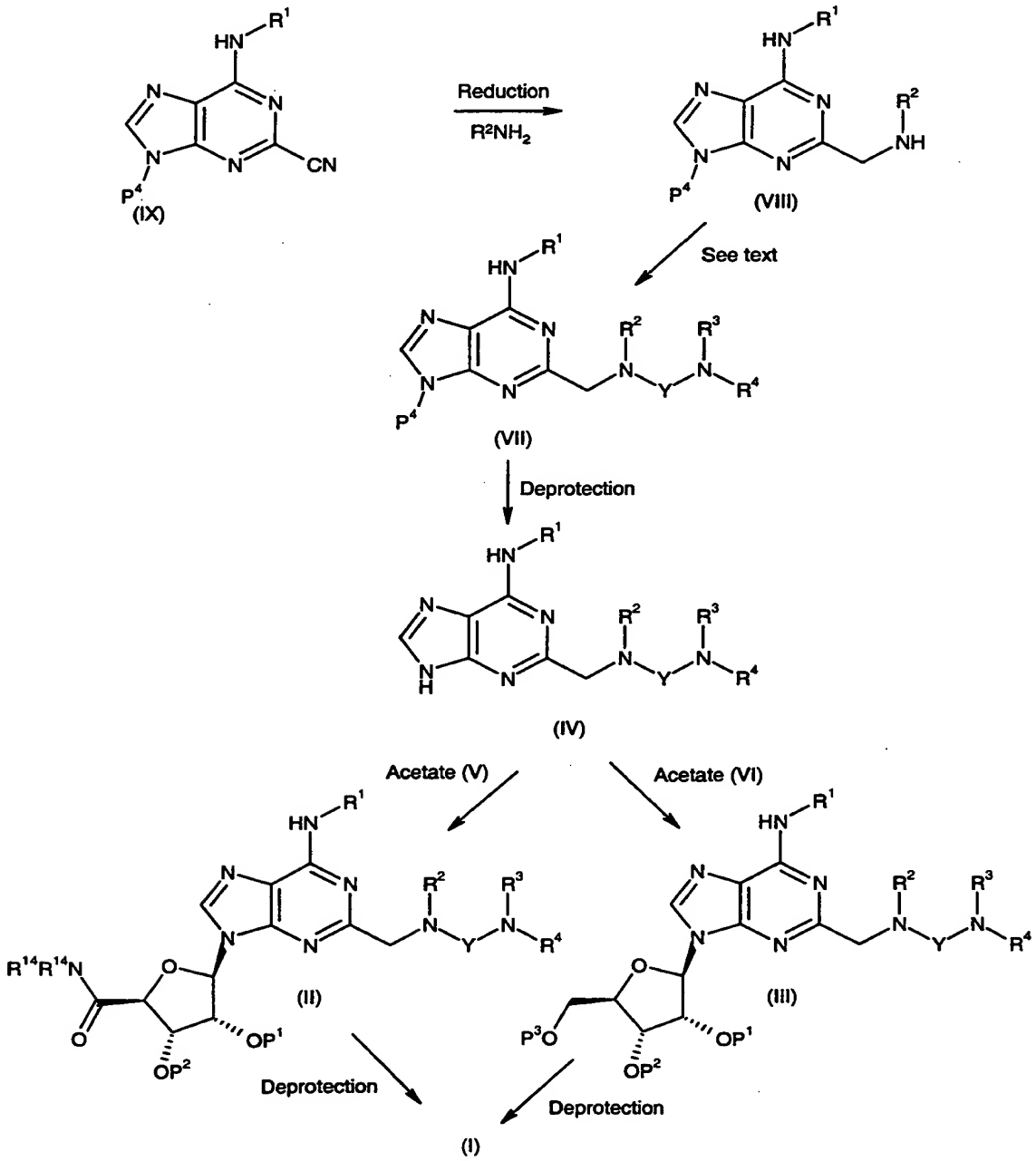
and pharmaceutically acceptable salts and solvates thereof.

All of the compounds of the formula (I) can be prepared by conventional routes such as by the procedures described in the general methods presented below or by the specific methods described in the Examples section, or by similar methods thereto. The present invention also encompasses any one or more of these processes for preparing the compounds of formula (I), in addition to any novel intermediates used therein.

In the following general methods, R^1, R^2, R^3, R^4, R^5, X and Y are as previously defined for a compound of the formula (I) unless otherwise stated.

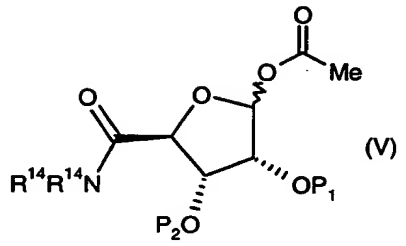
1. Compounds of the formula (I) in which X is $-CH_2-$ may be prepared according to the route shown in Scheme 1 wherein P^1, P^2, P^3 and P^4 each represent a protecting group.

Scheme 1



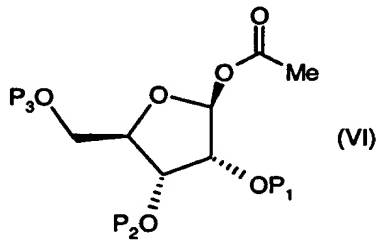
In Scheme 1, the compounds of the formula (I) in which X is $-CH_2-$ and R^5 is $CONR^{14}R^{14}$ may be prepared by the deprotection of a compound of the formula (II) in which protecting groups P^1 and P^2 may be the same or different and may optionally form part of the same protecting group. Alternatively, the compounds of the formula (I) in which X is $-CH_2-$ and R^5 is CH_2OH may be prepared by deprotection of a compound of the formula (III) wherein protecting groups P^1, P^2 and P^3 may be the same or different, P^1 and P^2 optionally forming part of the same protecting group. When deprotecting a compound of the formula (II) or a compound of the formula (III), the relevant protecting groups may be removed separately, progressing through one or more semi-protected intermediates, or together, or in any combination. Examples of suitable protecting groups will be apparent to the skilled person [see, for instance, 'Protecting groups in Organic Synthesis (Second Edition)', Theodora W. Green and Peter G. M. Wuts, John Wiley and Sons, 1991]. Preferred individual protecting groups are alkanoyl and aroyl. Preferred protecting groups where P^1 and P^2 form part of the same protecting group are where P^1 and P^2 taken together are C_1-C_6 alkylene. Particularly preferred individual protecting groups are acetyl and benzoyl. A particularly preferred protecting group where $P^1$and P^2 form part of the same protecting group is where P^1 and P^2 taken together are dimethylmethylene. Suitable conditions for the deprotection are well known in the art [see, for instance, 'Protecting groups in Organic Synthesis (Second Edition)', Theodora W. Green and Peter G. M. Wuts, John Wiley and Sons, 1991]. In a typical procedure, a solution of a compound of the formula (III), wherein P^1, P^2 and P^3 are each acetyl, in a suitable solvent, such as methanol, is treated with a nucleophilic reagent, such as ammonia or a primary amine, or a base such as potassium carbonate, typically at room temperature. In another typical procedure, a solution of a compound of the formula (II), wherein $P^1$and P^2 are each benzoyl, in a suitable solvent, such as methanol, is treated with a nucleophilic reagent, such as ammonia or a primary amine, or a base such as potassium carbonate, typically at a temperature from room temperature to 60 C.

Compounds of the formula (II) may be prepared by the reaction of a compound of the formula



(in which P^1 and P^2 are as defined above) with trimethylsilyl trifluoromethanesulfonate and a compound of the formula (IV) which has been derivatised with N,O-bis(trimethylsilyl)acetamide. In a typical procedure, the compound of the formula (IV) is heated in the presence of a suitable solvent, such as 1,1,1-trichloroethane, with N,O-bis(trimethylsilyl)acetamide at an elevated temperature, preferably at about 50 °C. The mixture is then allowed to cool and the solvent is evaporated. A solution of the residue in a suitable solvent, such as toluene, is treated with the compound of the formula (V) and trimethylsilyl trifluoromethanesulfonate and the mixture is heated, preferably under reflux, under a nitrogen atmosphere, to give the compound of the formula (II).

Compounds of the formula (III) may be prepared by the reaction of a compound of the formula

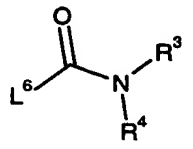


(in which P^1, P^2 and P^3 are as defined above) with trimethylsilyl trifluoromethanesulfonate and a compound of the formula (IV) which has been

derivatised with N,O-bis(trimethylsilyl)acetamide. In a typical procedure, the compound of the formula (IV) is heated in the presence of a suitable solvent, such as 1,1,1-trichloroethane, with N,O-bis(trimethylsilyl)acetamide at an elevated temperature, preferably at 50 °C. The mixture is then allowed to cool and the solvent is removed. A solution of the residue in a suitable solvent such as toluene is treated with the compound of the formula (VI) and trimethylsilyl trifluoromethanesulfonate and the mixture is heated, preferably under reflux, under a nitrogen atmosphere, to give the compound of the formula (III).

Compounds of the formula (IV) may be prepared by the deprotection of a compound of the formula (VII) wherein P^4 is a suitable protecting group. Examples of suitable protecting groups will be apparent to the skilled person [see, for instance, 'Protecting groups in Organic Synthesis (Second Edition)', Theodora W. Green and Peter G. M. Wuts, John Wiley and Sons, 1991]. A preferred protecting group is that in which P^4 represents tetrahydropyran-2-yl. Suitable conditions for the deprotection are well known in the art [see, for instance, 'Protecting groups in Organic Synthesis (Second Edition)', Theodora W. Green and Peter G. M. Wuts, John Wiley and Sons, 1991]. In a typical procedure, where P^4 is tetrahydropyran-2-yl, the protecting group is removed by treating a solution of the compound of the formula (VII) in a suitable solvent, such as methanol, with an acid such as hydrochloric acid, preferably 2M aqueous hydrochloric acid.

Compounds of the formula (VII) in which Y is CO may be prepared by the reaction of a compound of the formula



(X)

in which L^6 is a suitable leaving group, with a compound of the formula (VIII) in a suitable solvent, such as a mixture of toluene and isopropanol, typically at an elevated temperature, preferably under reflux. The leaving group L^6 is

preferably halo (e.g. chloro) or imidazol-1-yl, most preferably imidazol-1-yl. Compounds of the formula (X) wherein L^6 is imidazol-1-yl may be prepared by the reaction of a compound of the formula

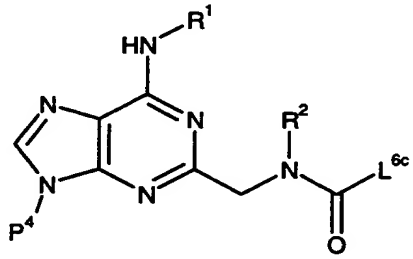
$$R^3R^4NH \text{ (XI)}$$

with 1,1'-carbonyldiimidazole. In a typical reaction a compound of the formula (XI) is added to a solution of 1,1'-carbonyldiimidazole in a suitable solvent such as dichloromethane. Compounds of the formula (XI) are either commercially available or may be prepared by standard techniques well known to persons skilled in the art. Other compounds of the formula (X) are either commercially available or easily prepared by methods well known to the person skilled in the art.

Alternatively, compounds of the formula (VII) in which Y is CO may be prepared by the reaction of a compound of the formula (VIII) with a compound of the formula

$$L^{6a}COL^{6b} \text{ (XA)}$$

in which L^{6a} and L^{6b} are suitable leaving groups, to form an intermediate of the formula



(VIIIA)

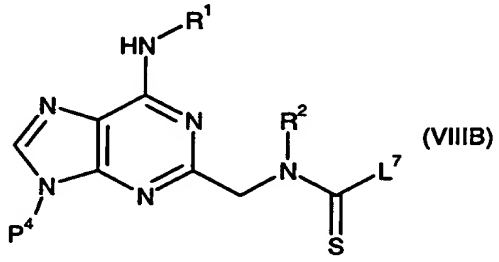
in which L^{6c} represents either of the leaving groups L^{6a} or L^{6b}, followed by the addition of a compound of the formula (XI) to the reaction mixture. Preferably,

L^{6a} and L^{6b} are each halo or imidazol-1-yl. Most preferably, L^{6a} and L^{6b} are each imidazol-1-yl. In a typical example, where L^{6a} and L^{6b} are each imidazol-1-yl, a solution of the compound of the formula (VIII) in a suitable solvent, such as dichloromethane, is treated with 1,1'-carbonyldiimidazole. The reaction mixture is stirred, preferably at room temperature, until thin layer chromatography (TLC) indicates a substantially complete reaction has occurred and then a compound of the formula (XI) is added to give the compound of the formula (VII).

Compounds of the formula (VII) in which Y is CS may be prepared by the reaction of a compound of the formula

$$L^1L^2C{=}S \quad (XII)$$

in which L^1 and L^2 are suitable leaving groups, with a compound of the formula (VIII), to form an intermediate of the formula



(VIIIB)

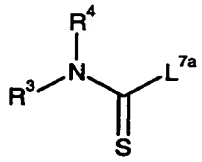
in which L^7 represents either of the leaving groups L^1 or L^2, followed by the addition of a compound of the formula (XI). The leaving groups L^1 and L^2 may be the same or different and are typically selected from -S(C_1-C_6 alkyl) or imidazol-1-yl. Preferably, L^1 and L^2 are each methylthio or imidazol-1-yl. In a typical procedure, a solution of the compound of the formula (XII) in a suitable solvent, such as ethanol, is treated with the compound of the formula (VIII), preferably at an elevated temperature, most preferably under reflux. When analysis by thin layer chromatography shows that a substantially complete

reaction has occurred, a compound of the formula (XI) is added and the reaction mixture is preferably heated, most preferably under reflux

Alternatively, compounds of the formula (VII) in which Y is CS may be prepared by the reaction of a compound of the formula

$$L^1L^2C{=}S \text{ (XII)}$$

in which L^1 and L^2 are as defined above, with a compound of the formula (XI), to form an intermediate of the formula



(VIIIBB)

in which L^{7a} represents either of the leaving groups L^1 or L^2, followed by the addition of a compound of the formula (VIII). In a typical procedure, a solution of the compound of the formula (XII) in a suitable solvent, such as ethanol, is treated with the compound of the formula (XI), preferably at an elevated temperature, most preferably under reflux. When analysis by thin layer chromatography shows that a substantially complete reaction has occurred, a compound of the formula (VIII) is added and the reaction mixture is preferably heated, most preferably under reflux.

Compounds of the formula (VII) in which Y is SO_2 may be prepared by the reaction of a compound of the formula

$$R^3R^4NSO_2L^3 \text{ (XIII)}$$

in which L^3 is a suitable leaving group, typically halo, with a compound of the formula (VIII), optionally in the presence of an acid acceptor. Preferably, L^3 is chloro. In a typical example, a solution of the compound of the formula (VIII) in a suitable solvent, such as pyridine, is treated with the compound of the formula

(XIII) and preferably heated, most preferably at 90°C. Compounds of the formula (XIII) may be prepared by treating a compound of the formula

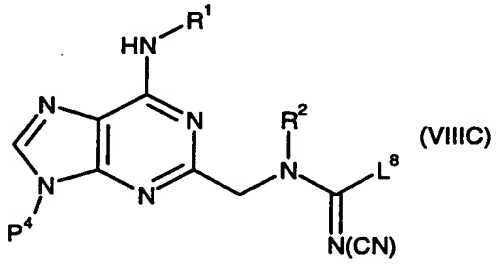
$$R^3R^4NSO_3H \text{ (XIV)}$$

with an activating agent. In a typical example, where L^3 is chloro, a solution of a compound of the formula (XIV), in a suitable solvent such as toluene, is treated with PCl_5 and heated, preferably under reflux. Compounds of the formula (XIV) may be prepared by treating a compound of the formula (XI) with chlorosulphonic acid. In a typical procedure, a solution of the compound of the formula (XI) in a suitable solvent, such as dichloromethane, is treated with chlorosulphonic acid, optionally in the presence of a proton acceptor such as triethylamine.

Compounds of the formula (VII) in which Y is C=N(CN) may be prepared by the reaction of a compound of the formula

$$L^4L^5C{=}N(CN) \text{ (XV)}$$

in which L^4 and L^5 are suitable leaving groups, with a compound of the formula (VIII), to form an intermediate of the formula



(VIIIC)

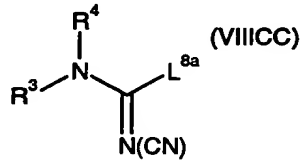
in which L^8 represents either of leaving groups L^4 or L^5, followed by the addition of a compound of the formula (XI). The leaving groups L^4 and L^5 may be the same or different and are typically selected from halo and -S(C_1-C_6 alkyl).

Preferably, L^4 and L^5 are each methythio. In a typical procedure, where L^4 and L^5 are each methylthio, a solution of a compound of the formula (VIII) in a suitable solvent, such as ethanol, is treated with dimethylcyanothioimidocarbamate, preferably at room temperature. When a substantially complete reaction is indicated by thin layer chromatography (TLC), a compound of the formula (XI) is added and the reaction mixture is preferably heated, most preferably under reflux.

Alternatively, compounds of the formula (VII) in which Y is C=N(CN) may be prepared by the reaction of a compound of the formula

$$L^4L^5C{=}N(CN) \quad (XV)$$

in which L^4 and L^5 are as defined above, with a compound of the formula (XI), to form an intermediate of the formula



(VIIICC)

in which L^{8a} represents either of the leaving groups L^4 or L^5, followed by the addition of a compound of the formula (VIII). In a typical procedure, where L^4 and L^5 are each methylthio, a solution of a compound of the formula (XI) in a suitable solvent, such as ethanol, is treated with dimethylcyanothioimidocarbamate, preferably at room temperature. When a substantially complete reaction is indicated by thin layer chromatography (TLC), a compound of the formula (VIII) is added and the reaction mixture is preferably heated, most preferably under reflux.

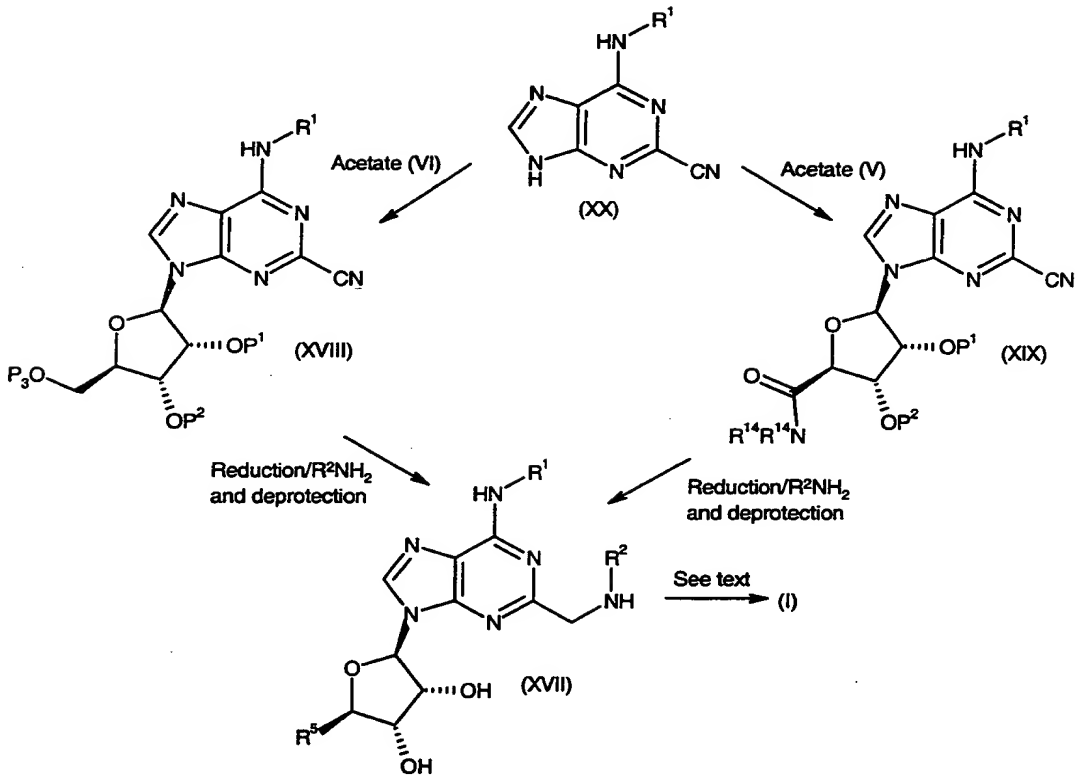
Compounds of the formula (VIII) may be prepared by the reduction of a compound of the formula (IX) with a suitable reducing agent, preferably a palladium catalyst and hydrogen gas, in the presence of a compound of the formula

R^2NH_2 (XVI).

In a typical procedure, where R^2 = H, a compound of the formula (IX) is dissolved in a suitable solvent, such as ethanol, which has been saturated with ammonia gas, a palladium catalyst such as 10% w/w palladium on carbon is added and the reaction mixture is stirred under an atmosphere of hydrogen gas, typically at a pressure of 414kPa (60psi). Compounds of the formula (IX) are known in the art (see, for example, WO-A-00/23457). Compounds of the formula (XVI) are either commercially available or readily prepared by methods well known to those skilled in the art.

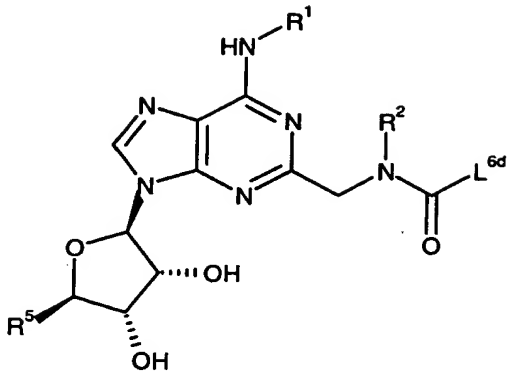
2. Compounds of the formula (I) in which X is $-CH_2-$ may also be prepared according to the route shown in Scheme 2, wherein P^1, P^2 and P^3 are as defined above.

Scheme 2



In Scheme 2, the compounds of the formula (I) in which X is $-CH_2-$ and Y is CO may be prepared by the reaction of a compound of the formula (X), in which L^6 is as defined above, with a compound of the formula (XVII) in a suitable solvent, such as a mixture of toluene and isopropanol, preferably at an elevated temperature, most preferably under reflux.

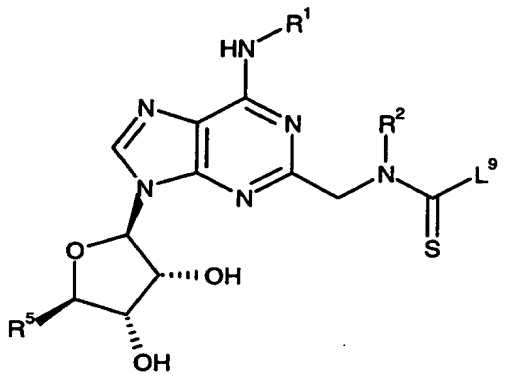
Alternatively, compounds of the formula (I) in which X is $-CH_2-$ and Y is CO may be prepared by the reaction of a compound of the formula (XVII) with a compound of the formula (XA), in which L^{6a} and L^{6b} are as defined above, to form an intermediate of the formula



(XVIIA)

in which L^{6d} represents either of protecting groups L^{6a} or L^{6b}. The intermediate (XVIIA) is reacted with a compound of the formula (XI) to provide a compound of the formula (I). In a typical example, where L^{6a} and L^{6b} are each imidazol-1-yl, a solution of the compound of the formula (XVII) in a suitable solvent, such as dichloromethane, is treated with 1,1'-carbonyldiimidazole. The reaction mixture is stirred, preferably at room temperature, until thin layer chromatography (TLC) indicates a substantially complete reaction has occurred and then a compound of the formula (XI) is added to give the compound of the formula (I).

Compounds of the formula (I) in which X is $-CH_2-$ and Y is CS may be prepared by the reaction of a compound of the formula (XII) in which L^1 and L^2 are as defined above, with a compound of the formula (XVII), to form an intermediate of the formula



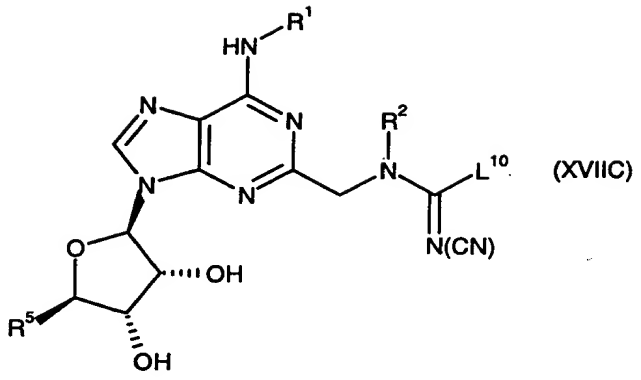
(XVIIB)

in which L^9 represents either of the leaving groups L^1 or L^2. The intermediate of the formula (XVIIB) is reacted with a compound of the formula (XI) to provide a compound of the formula (I). In a typical procedure, a solution of the compound of the formula (XVII) in a suitable solvent, such as ethanol, is treated with the compound of the formula (XII), preferably at an elevated temperature, most preferably under reflux. When analysis by thin layer chromatography shows that a substantially complete reaction has occurred, a compound of the formula (XI) is added and the reaction mixture is preferably heated, most preferably under reflux.

Alternatively, compound of the formula (I) in which X is $-CH_2-$ and Y is CS may be prepared by the reaction of a compound of the formula (VIIIBB) in which L^7 is as defined above with a compound of the formula (XVII). In a typical procedure, a solution of the compound of the formula (VIIIBB) in a suitable solvent, such as ethanol, is treated with the compound of the formula (XVII) and preferably heated, most preferably under reflux.

Compounds of the formula (I) in which X is $-CH_2-$ and Y is SO_2 may be prepared by the reaction of a compound of the formula (XIII), in which L^3 is as defined above, with a compound of the formula (XVII), optionally in the presence of an acid acceptor. In a typical procedure, a solution of the compound of the formula (XVII) in a suitable solvent, such as pyridine, is treated with the compound of the formula (XIII) and heated, typically at 90 °C.

Compounds of the formula (I) in which X is $-CH_2-$ and Y is C=N(CN) may be prepared by the reaction of a compound of the formula (XV) in which L^4 and L^5 are as defined above, with a compound of the formula (XVII), to form an intermediate of the formula

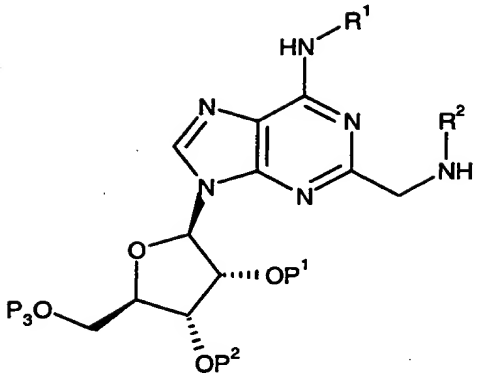


(XVIIC)

in which L^{10} represents either of L^4 or L^5. The intermediate of the formula (XVIIC) is reacted with a compound of the formula (XI) to give a compound of the formula (I). In a typical procedure, where L^4 and L^5 are each methylthio, a solution of a compound of the formula (XVII) in a suitable solvent, such as ethanol, is treated with dimethylcyanothioimidocarbamate, preferably at room temperature. When a substantially complete reaction is indicated by thin layer chromatography (TLC), a compound of the formula (XI) is added and the reaction mixture is preferably heated, most preferably under reflux, to give the compound of the formula (I).

Alternatively, compounds of the formula (I) in which X is $-CH_2-$ and Y is C=N(CN) may be prepared by the reaction of a compound of the formula (VIIICC), in which L^8 is as defined above, with a compound of the formula (XVII). In a typical procedure, a solution of the compound of the formula (VIIICC) in a suitable solvent, such as ethanol, is treated with the compound of the formula (XVII) and preferably heated, most preferably under reflux.

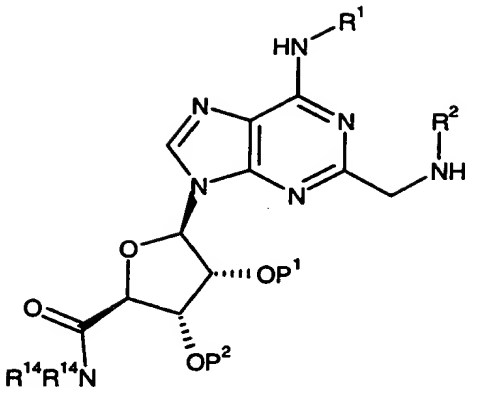
Compounds of the formula (XVII) in which R^5 is CH_2OH may be prepared by reducing a compound of the formula (XVIII) in the presence of a compound of the formula (XVI) to give a compound of the formula



(XVIIIA)

and deprotecting the compound of the formula (XVIIIA). Alternatively, if the protecting groups employed are readily removed by the conditions chosen for the reduction, then the reducing and deprotecting steps will usually be performed together to give a compound of the formula (XVII) directly from a compound of the formula (XVIII). The reduction is carried out using a suitable reducing agent, such as a palladium catalyst and hydrogen gas, in the presence of a compound of formula (XVI). Suitable conditions for the deprotection are well known in the art [see, for instance, 'Protecting groups in Organic Synthesis (Second Edition)', Theodora W. Green and Peter G. M. Wuts, John Wiley and Sons, 1991]. In a typical procedure, where R^2 is H, P^1, P^2 and P^3 are each acetyl and the reducing and deprotecting steps are carried out together, a compound of the formula (XVIII) is dissolved in a suitable solvent, such as ethanol, which has been saturated with ammonia gas, a palladium catalyst, such as 10% w/w palladium on carbon, is added and the reaction is stirred under an atmosphere of hydrogen gas, typically at a pressure of 414kPa (60psi).

Compounds of the formula (XVII) in which R^5 is $CONR^{14}R^{14}$ may be prepared by reducing a compound of the formula (XIX) in the presence of a compound of the formula (XVI) to give a compound of the formula



(XIXA)

and deprotecting the compound of the formula (XIXA). Alternatively, if the protecting groups employed are readily removed by the conditions chosen for the reduction, then the reducing and deprotecting steps will usually be performed together to give a compound of the formula (XVII) directly from a compound of the formula (XIX). The reduction is carried out using a suitable reducing agent, such as a palladium catalyst and hydrogen gas, in the presence of a compound of formula (XVI). Suitable conditions for the deprotection are well known in the art [see, for instance, 'Protecting groups in Organic Synthesis (Second Edition)', Theodora W. Green and Peter G. M. Wuts, John Wiley and Sons, 1991]. In a typical procedure, where R^2 is H, P^1 and P^2 are each benzoyl and the reducing and deprotecting are carried out together, a compound of the formula (XIX) is dissolved in a suitable solvent, such as ethanol, which has been saturated with ammonia gas, a palladium catalyst, such as 10% w/w palladium on carbon, is added and the reaction is stirred under an atmosphere of hydrogen gas, typically at a pressure of 414kPa (60psi).

Compounds of the formula (XVIII) may be prepared by the reaction of an acetate of the formula (VI) with trimethylsilyl trifluoromethanesulfonate and a compound of the formula (XX) which has been derivatised with N,O-bis(trimethylsilyl)acetamide. In a typical procedure, a compound of the formula

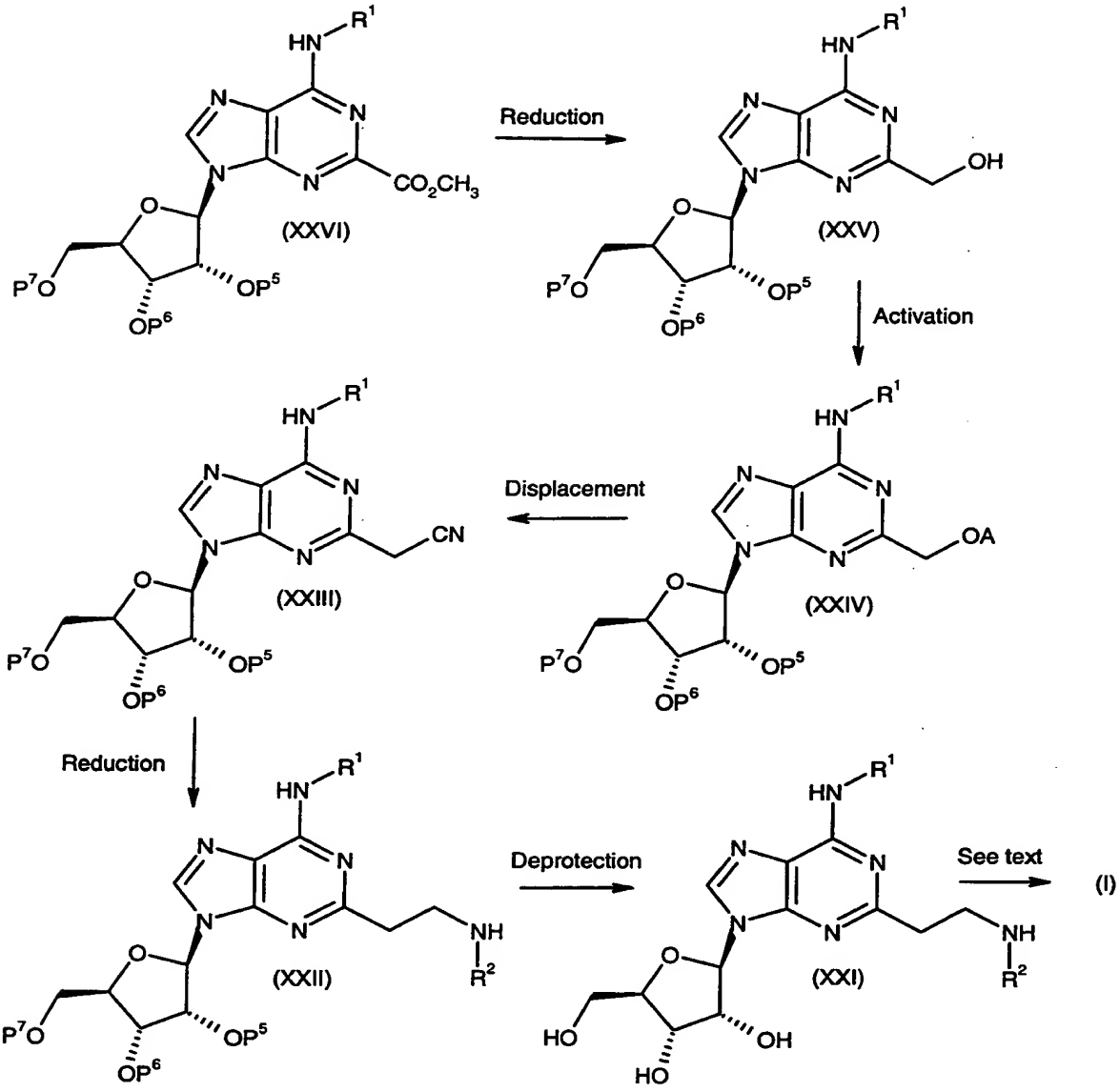
(XX) is heated, in the presence of a suitable solvent, such as 1,1,1-trichloroethane, with N,O-bis(trimethylsilyl)acetamide, preferably under reflux. The mixture is then allowed to cool and the solvent is removed. A solution of the residue in a suitable solvent, such as toluene, is treated with the acetate of the formula (VI) and trimethylsilyl trifluoromethanesulfonate. The mixture so formed is preferably heated, most preferably under reflux, under a nitrogen atmosphere, to give the compound of the formula (XVIII).

Compounds of the formula (XIX) may be prepared by the reaction of an acetate of the formula (V) with a compound of the formula (XX) and iodine. In a typical example, a compound of the formula (XX), a compound of the formula (V) and iodine are heated together, preferably at 150°C, under reduced pressure, preferably at 7 kPa (1 psi).

Compounds of the formula (XX) are known in the art (see, for example, WO-A-00/23457).

3. Compounds of the formula (I) in which X is $-CH_2CH_2-$ and R^5 is CH_2OH may be prepared according to the route shown in Scheme 3 wherein P^5, P^6 and P^7 each represent a protecting group and A represents an activating group.

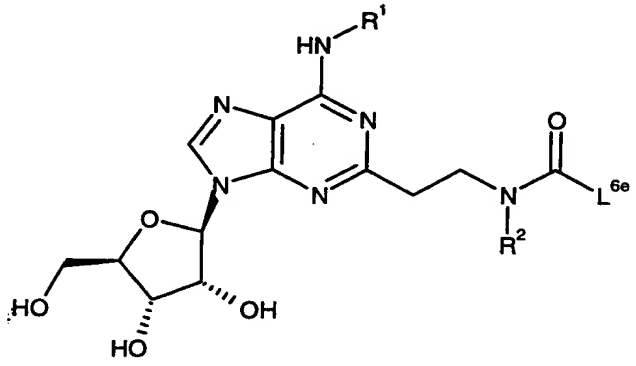
Scheme 3



In Scheme 3, the compounds of the formula (I) in which X is $-CH_2CH_2-$, R^5 is CH_2OH and Y is CO may be prepared by the reaction of compound of the formula (X), in which L^6 is as defined above, with a compound of the formula (XXI) in a suitable solvent, such as a mixture of toluene and isopropanol, typically at an elevated temperature, preferably under reflux.

Alternatively, compounds of the formula (I) in which X is $-CH_2CH_2-$, R^5 is CH_2OH and Y is CO may be prepared by the reaction of a compound of the

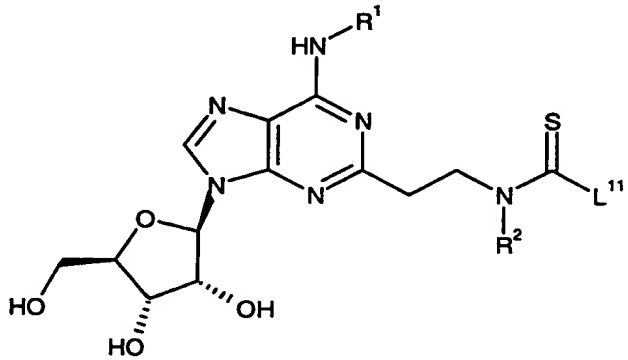
formula (XXI) with a compound of the formula (XA), in which L^{6a} and L^{6b} are as defined above, to form an intermediate of the formula



(XXIA)

in which L^{6e} represents either of leaving groups L^{6a} or L^{6b}. The intermediate (XXIA) is reacted with a compound of the formula (XI) to provide a compound of the formula (I). In a typical example, where L^{6a} and L^{6b} are each imidazol-1-yl, a solution of the compound of the formula (XXI) in a suitable solvent, such as dichloromethane, is treated with 1,1'-carbonyldiimidazole. The reaction mixture is stirred, preferably at room temperature, until thin layer chromatography (TLC) indicates a substantially complete reaction has occurred and then a compound of the formula (XI) is added to give the compound of the formula (I).

Compounds of the formula (I) in which X is $-CH_2CH_2-$, R^5 is CH_2OH and Y is CS may be prepared by the reaction of a compound of the formula (XII) in which L^1 and L^2 are as defined above, with a compound of the formula (XXI), to form an intermediate of the formula



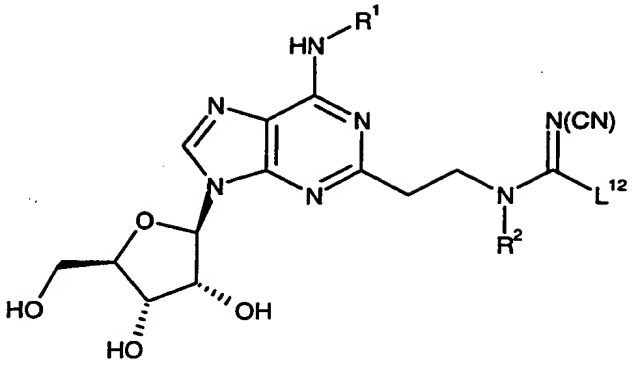
(XXIB)

in which L^{11} represents either of leaving groups L^1 or L^2. The intermediate of the formula (XXIB) is reacted with a compound of the formula (XI) to provide a compound of the formula (I). In a typical procedure, a solution of the compound of the formula (XII) in a suitable solvent, such as ethanol, is treated with the compound of the formula (XXI), preferably at an elevated temperature, most preferably under reflux. When analysis by thin layer chromatography shows that a substantially complete reaction has occurred, the compound of the formula (XI) is added and the reaction mixture is preferably heated, most preferably under reflux.

Alternatively, compounds of the formula (I) in which X is $-CH_2CH_2-$, R^5 is CH_2OH and Y is CS may be prepared by the reaction of a compound of the formula (VIIIBB), in which L^7 is as defined above, with a compound of the formula (XXI). In a typical procedure, a solution of the compound of the formula (VIIIBB) in a suitable solvent, such as ethanol, is treated with the compound of the formula (XXI) and preferably heated, most preferably under reflux.

Compounds of the formula (I) in which X is $-CH_2CH_2-$, R^5 is CH_2OH and Y is SO_2 may be prepared by the reaction of a compound of the formula (XIII), in which L^3 is as defined above, with a compound of formula (XXI), optionally in the presence of an acid acceptor. In a typical procedure, a solution of the compound of the formula (XIII) in a suitable solvent, such as pyridine, is treated with the compound of the formula (XXI) and heated, typically at 90°C.

Compounds of the formula (I) in which X is $-CH_2CH_2-$, R^5 is CH_2OH and Y is C=N(CN) may be prepared by the reaction of a compound of the formula (XV) in which L^4 and L^5 are as defined above, with a compound of the formula (XXI), to form an intermediate of the formula



(XXIC)

in which L^{12} represents either of leaving groups L^4 or L^5. The intermediate of the formula (XXIC) is reacted with a compound of the formula (XI) to provide a compound of the formula (I). In a typical procedure, where L^4 and L^5 are each methylthio, a solution of a compound of the formula (XXI) in a suitable solvent, such as ethanol, is treated with dimethylcyanothioimidocarbamate, preferably at room temperature. When a substantially complete reaction is indicated by thin layer chromatography (TLC), a compound of the formula (XI) is added and the reaction mixture is preferably heated, most preferably under reflux.

Alternatively, compounds of the formula (I) in which X is $-CH_2CH_2-$, R^5 is CH_2OH and Y is C=N(CN) may be prepared by the reaction of a compound of the formula (VIIICC), in which L^8 is as defined above, with a compound of the formula (XXI). In a typical procedure, a solution of the compound of the formula (VIIICC) in a suitable solvent, such as ethanol, is treated with the compound of the formula (XXI) and preferably heated, most preferably under reflux.

Compounds of the formula (XXI) may be prepared by the deprotection of a compound of the formula (XXII), in which protecting groups P^5, P^6 and P^7 may be the same or different, P^5 and P^6 optionally forming part of the same protecting group. Examples of suitable protecting groups will be apparent to the skilled person [see, for instance, 'Protecting groups in Organic Synthesis (Second Edition)', Theodora W. Gr en and Peter G. M. Wuts, John Wiley and Sons, 1991]. Preferred individual protecting groups are tri(C_1-C_6)alkylsilyl, di(C_1-

C_6)alkylphenylsilyl and (C_1-C_6)alkyldiphenylsilyl. Preferred protecting groups where P^5 and P^6 form part of the same protecting group are where P^5 and P^6 taken together are C_1-C_6 alkylene. Particularly preferred individual protecting groups are tert-butyldimethylsilyl and triethylsilyl. A particularly preferred protecting group where $P^5$and P^6 form part of the same protecting group is where P^5 and P^6 taken together are dimethylmethylene. Suitable conditions for the deprotection are well known in the art [see, for instance, 'Protecting groups in Organic Synthesis (Second Edition)', Theodora W. Green and Peter G. M. Wuts, John Wiley and Sons, 1991]. In a typical procedure, a solution of a compound of the formula (XXII), wherein P^5, P^6 and P^7 are each tert-butyldimethylsilyl, in a suitable solvent, such as methanol, is treated with an acid such as hydrochloric acid, typically at room temperature.

Compounds of the formula (XXII) may be prepared by the reduction of a compound of the formula (XXIII) with a suitable reducing agent in the presence of a compound of the formula (XVI). A preferred reducing agent is Raney nickel, optionally in the presence of hydrogen gas. In a typical procedure, where R^2 = H, the compound of the formula (XXIII) is dissolved in a suitable solvent, such as ethanol, which has been saturated with ammonia gas, Raney nickel is added and the reaction mixture is shaken, preferably at room temperature.

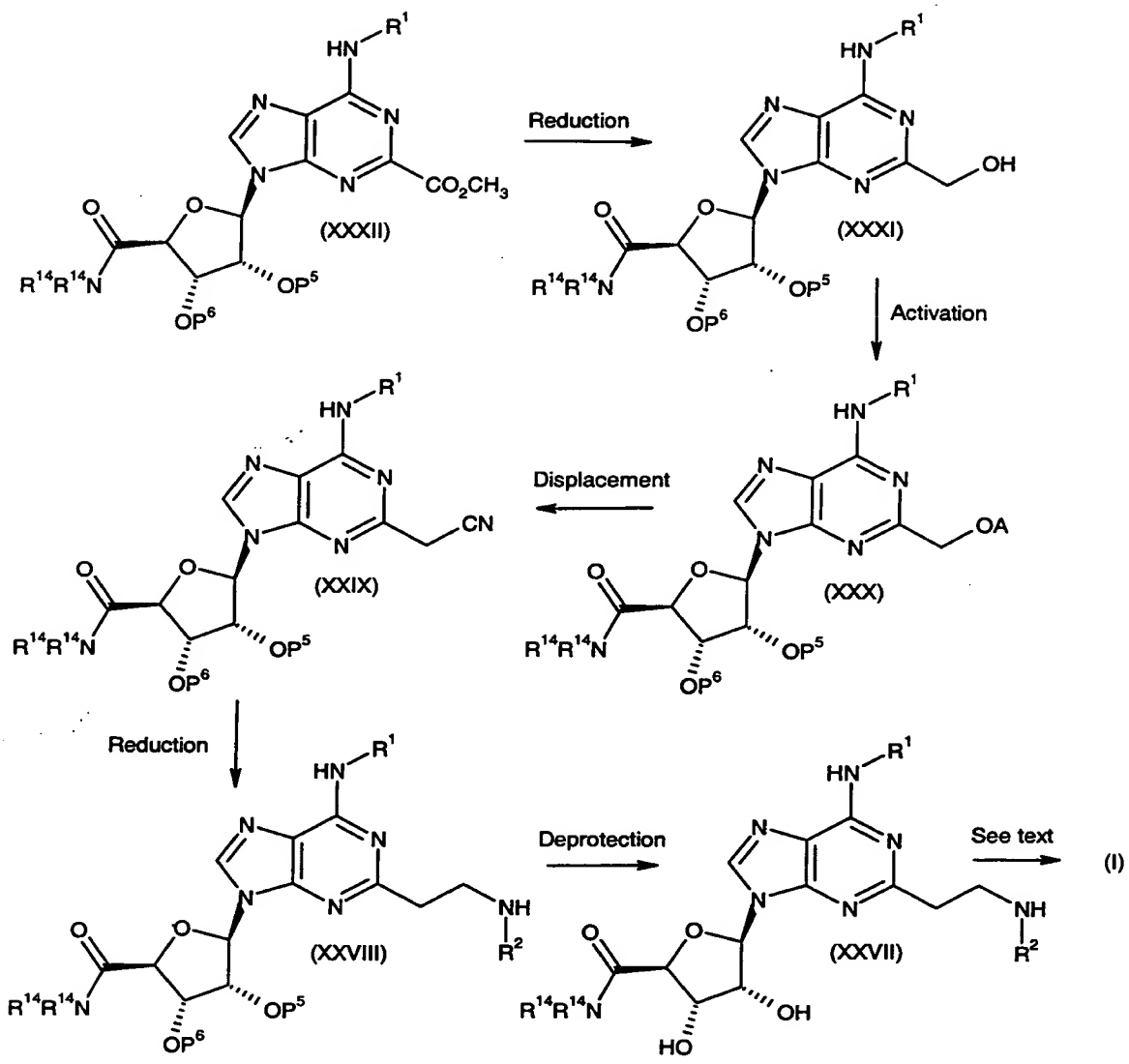
Compounds of the formula (XXIII) may be prepared by the displacement of a leaving group 'OA', in which A is an activating group, from a compound of the formula (XXIV) with cyanide anion. In a typical example, a solution of the compound of the formula (XXIV) in a suitable solvent, such as N,N-dimethylformamide, is treated with a source of cyanide ion, such as potassium cyanide to give the compound of the formula (XXIII). Examples of suitable choices for A will be apparent to the skilled man [see for example 'Advanced Organic Chemistry (Third Edition)', Jerry March, Wiley-Interscience, 1985]. Preferably, A is (C_1-C_6)alkylsulphonyl, phenylsulphonyl or ((C_1-C_6)alkylphenyl)sulphonyl. Most preferably, 'OA' is methylsulphonyl.

Compounds of the formula (XXIV) may be prepared by the activation of the free hydroxyl in a compound of the formula (XXV). In a typical example, where A is methylsulphonyl, a solution of the compound of the formula (XXV) in a suitable solvent, such as dichloromethane, is treated with methanesulfonyl chloride in the presence of a proton acceptor such as triethylamine.

Compounds of the formula (XXV) may be prepared by the reduction of an ester of the formula (XXVI) with a suitable reducing agent, such as lithium borohydride, in a suitable solvent, such as tetrahydrofuran.

4. Compounds of the formula (I) in which X is $-CH_2CH_2-$ and R^5 is $CONR^{14}R^{14}$ may be prepared according to the route shown in Scheme 4, wherein A, P^5 and P^6 are as defined above.

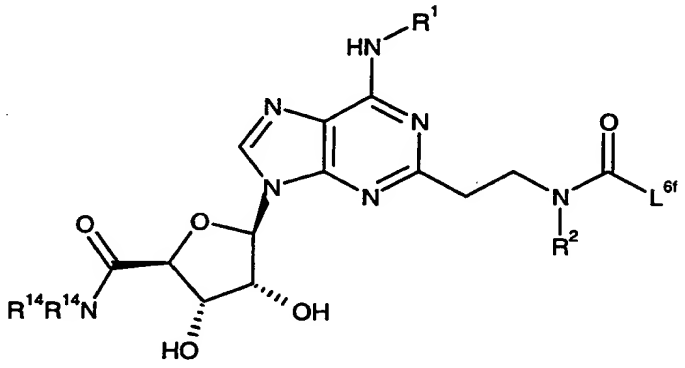
Scheme 4



In Scheme 4, the compounds of the formula (I) in which X is $-CH_2CH_2-$, R^5 is $CONR^{14}R^{14}$ and Y is CO may be prepared by the reaction of a compound of the formula (X), in which L^6 is as defined above, with a compound of the formula (XXVII) in a suitable solvent, such as a mixture of toluene and isopropanol, typically at an elevated temperature, preferably under reflux.

Alternatively, compounds of the formula (I) in which X is $-CH_2CH_2-$, R^5 is $CONR^{14}R^{14}$ and Y is CO may be prepared by the reaction of a compound of the

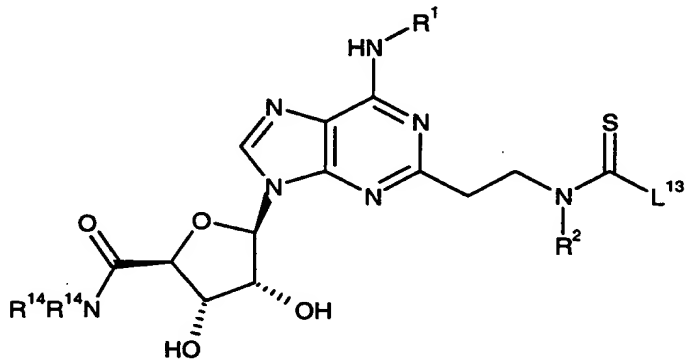
formula (XXVII) with a compound of the formula (XA), in which L^{6a} and L^{6b} are as defined above, to form an intermediate of the formula



(XXVIIA)

in which L^{6f} represents either of leaving groups L^{6a} or L^{6b}. The intermediate of the formula (XXVIIA) is reacted with a compound of the formula (XI) to form a compound of the formula (I). In a typical example, a solution of the compound of the formula (XXVII) in a suitable solvent, such as dichloromethane, is treated with the compound of the formula (XA). The reaction mixture is stirred, preferably at room temperature, until thin layer chromatography (TLC) indicates a substantially complete reaction has occurred and then a compound of the formula (XI) is added to give the compound of the formula (I).

Compounds of the formula (I) in which X is $-CH_2CH_2-$, R^5 is $CONR^{14}R^{14}$ and Y is CS may be prepared by the reaction of a compound of the formula (XII) in which L^1 and L^2 are as defined above, with a compound of the formula (XXVII), to form an intermediate of the formula



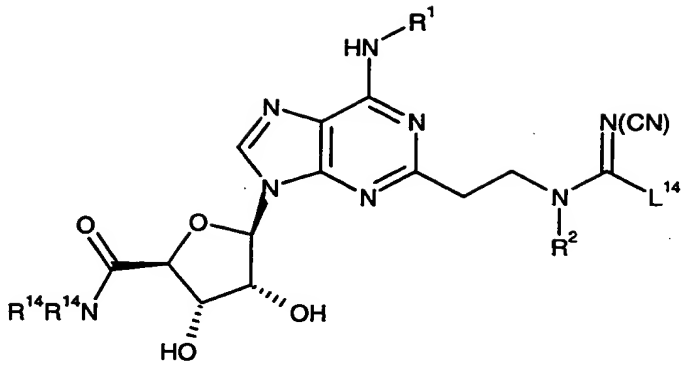
(XXVIIB)

in which L^{13} represents either of leaving groups L^1 or L^2. The intermediate of the formula (XXVIIB) is reacted with a compound of the formula (XI) to provide a compound of the formula (I). In a typical procedure, a solution of the compound of the formula (XII) in a suitable solvent, such as ethanol, is treated with the compound of the formula (XXVII), typically at an elevated temperature. Preferably, the reaction mixture is heated under reflux. When analysis by thin layer chromatography shows that a substantially complete reaction has occurred, the compound of the formula (XI) is added and the reaction mixture is preferably heated, most preferably under reflux.

Alternatively, compounds of the formula (I) in which X is $-CH_2CH_2-$, R^5 is $CONR^{14}R^{14}$ and Y is CS may be prepared by the reaction of a compound of the formula (VIIIBB), in which L^7 is as defined above, with a compound of the formula (XXVII). In a typical procedure, a solution of the compound of the formula (VIIIBB) in a suitable solvent, such as ethanol, is treated with the compound of the formula (XXVII), typically at an elevated temperature. Preferably, the reaction mixture is heated under reflux.

Compounds of the formula (I) in which X is $-CH_2CH_2-$, R^5 is $CONR^{14}R^{14}$ and Y is SO_2 may be prepared by the reaction of a compound of the formula (XIII) in which L^3 is as defined above with a compound of the formula (XXVII). In a typical example, a solution of the compound of the formula (XXVII) in a suitable solvent, such as pyridine, is treated with the compound of the formula (XIII) and heated, typically at 90°C.

Compounds of the formula (I) in which X is $-CH_2CH_2-$, R^5 is $CONR^{14}R^{14}$ and Y is C=N(CN) may be prepared by the reaction of a compound of the formula (XV) in which L^4 and L^5 are as defined above, with a compound of the formula (XXVII), to form an intermediate of the formula



(XXVIIC)

in which L^{14} represents either of leaving groups L^4 or L^5. The intermediate of the formula (XXVIIC) is reacted with a compound of the formula (XI) to provide a compound of the formula (I). In a typical procedure, where L^4 and L^5 are each methylthio, a solution of a compound of the formula (XXVII) in a suitable solvent, such as ethanol, is treated with dimethylcyanothioimidocarbamate, preferably at room temperature. When a substantially complete reaction is indicated by thin layer chromatography (TLC), a compound of the formula (XI) is added and the reaction mixture is preferably heated, most preferably under reflux.

Alternatively, compounds of the formula (I) in which X is $-CH_2CH_2-$, R^5 is $CONR^{14}R^{14}$ and Y is C=N(CN) may be prepared by the reaction of a compound of the formula (VIIICC), in which L^8 is as defined above, with a compound of the formula (XXVII). In a typical procedure, a solution of the compound of the formula (VIIICC) in a suitable solvent, such as ethanol, is treated with the compound of the formula (XXVII) and preferably heated, most preferably under reflux.

Compounds of the formula (XXVII) may be prepared by the deprotection of a compound of the formula (XXVIII). Suitable conditions for the deprotection are well known in the art [see, for instance, 'Protecting groups in Organic Synthesis (Second Edition)', Theodora W. Green and Peter G. M. Wuts, John Wiley and

Sons, 1991]. In a typical procedure, a solution of a compound of the formula (XXVIII), wherein P^5 and P^6 are each tert-butyldimethylsilyl, in a suitable solvent, such as methanol, is treated with an acid such as hydrochloric acid, typically at room temperature.

Compounds of the formula (XXVIII) may be prepared by the reduction of a compound of the formula (XXIX) with a suitable reducing agent in the presence of a compound of the formula (XVI). A preferred reducing agent is Raney nickel, optionally in the presence of hydrogen gas. In a typical example, where R^2 = H, a compound of the formula (XXIX) is dissolved in a suitable solvent, such as ethanol, which has been saturated with ammonia gas, Raney nickel is added and the reaction mixture is shaken, preferably at room temperature.

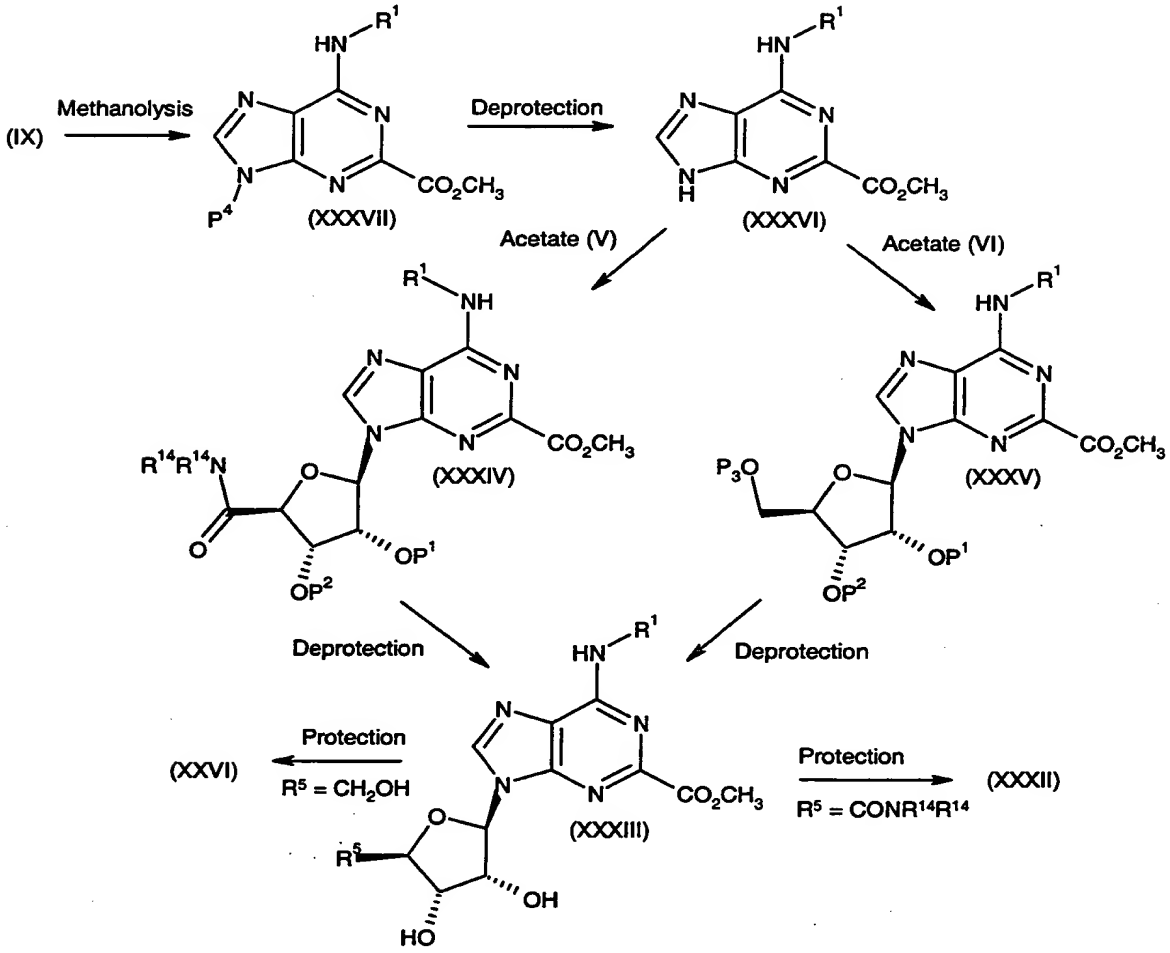
Compounds of the formula (XXIX) may be prepared by the displacement of a leaving group 'OA', from a compound of the formula (XXX) with cyanide anion. In a typical example, a solution of the compound of the formula (XXX) in a suitable solvent, such as N,N-dimethylformamide, is treated with a source of cyanide ion, such as potassium cyanide, to give the compound of the formula (XXIX).

Compounds of the formula (XXX) may be prepared by the activation of the free hydroxyl in a compound of the formula (XXXI). In a typical example, where A is methylsulphonyl, a solution of the compound of the formula (XXXI) in a suitable solvent, such as dichloromethane, is treated with methanesulfonyl chloride in the presence of a proton acceptor such as triethylamine.

Compounds of the formula (XXXI) may be prepared by the reduction of an ester of the formula (XXXII) with a suitable reducing agent, such as lithium borohydride, in a suitable solvent, such as tetrahydrofuran.

Scheme 5, wherein P^1, P^2, P^3 and P^4 are as defined above, illustrates the preparation of compounds of the formula (XXVI) and compounds of the formula (XXXII) used in Schemes 3 and 4 respectively.

Scheme 5



In Scheme 5, compounds of the formula (XXVI) may be prepared by the protection of a compound of the formula (XXXIII) in which R^5 is CH_2OH. Suitable conditions for the protection are well known to the skilled person [see, for instance, 'Protecting groups in Organic Synthesis (Second Edition)', Theodora W. Green and Peter G. M. Wuts, John Wiley and Sons, 1991]. In a typical example, where P^5, P^6 and P^7 are each tert-butyldimethylsilyl, a solution of the compound of the formula (XXXIII), in a suitable solvent such as N,N-

dimethylformamide, is treated with tert-butyldimethylsilylchloride and a suitable proton acceptor such as imidazole.

Compounds of the formula (XXXII) may be prepared by the protection of a compound of the formula (XXXIII) in which R^5 is $CONR^{14}R^{14}$. Suitable conditions for the protection are well known to the skilled person [see, for instance, 'Protecting groups in Organic Synthesis (Second Edition)', Theodora W. Green and Peter G. M. Wuts, John Wiley and Sons, 1991]. In a typical example, where P^5 and P^6 are each tert-butyldimethylsilyl, a solution of the compound of the formula (XXXIII), in a suitable solvent such as N,N-dimethylformamide, is treated with tert-butyldimethylsilylchloride and a suitable proton acceptor such as imidazole.

Compounds of the formula (XXXIII) may be prepared by the deprotection of a compound of the formula (XXXIV), where R^5 is $CONR^{14}R^{14}$, or the deprotection of a compound of the formula (XXXV), where R^5 is CH_2OH. Suitable conditions for both deprotections are well known to the skilled person [see, for instance, 'Protecting groups in Organic Synthesis (Second Edition)', Theodora W. Green and Peter G. M. Wuts, John Wiley and Sons, 1991]. In a typical procedure, where P^1, P^2 and, where appropriate, P^3 are each acetyl, a solution of the compound of the formula (XXXIV) or the compound of the formula (XXXV), as the case may be, in a suitable solvent, such as methanol, is treated with a nucleophile such as ammonia or a primary amine, or a base such as potassium carbonate, typically at room temperature.

Compounds of the formula (XXXIV) may be prepared by the reaction of a compound of the formula (V) with trimethylsilyl trifluoromethanesulfonate and a compound of the formula (XXXVI) which has been derivatised with N,O-bis(trimethylsilyl)acetamide. In a typical procedure, the compound of the formula (XXXVI) is heated in the presence of a suitable solvent, such as 1,1,1-trichloroethane, with N,O-bis(trimethylsilyl)acetamide at an elevated temperature, preferably under reflux. The mixture is th n allowed to cool and

the solvent is removed. A solution of the residue in a suitable solvent, such as toluene, is treated with the compound of the formula (V) and trimethylsilyl trifluoromethanesulfonate and the mixture is heated, preferably under reflux, under a nitrogen atmosphere, to give the compound of the formula (XXXIV).

Compounds of the formula (XXXV) may be prepared by the reaction of a compound of the formula (VI) with trimethylsilyl trifluoromethanesulfonate and a compound of the formula (XXXVI) which has been derivatised with N,O-bis(trimethylsilyl)acetamide. In a typical procedure, the compound of the formula (XXXVI) is heated in the presence of a suitable solvent, such as 1,1,1-trichloroethane, with N,O-bis(trimethylsilyl)acetamide at an elevated temperature, preferably under reflux. The mixture is then allowed to cool and the solvent is removed. A solution of the residue in a suitable solvent, such as toluene, is treated with the compound of the formula (VI) and trimethylsilyl trifluoromethanesulfonate and the mixture is heated, preferably under reflux, under a nitrogen atmosphere, to give the compound of the formula (XXXV).

Compounds of the formula (XXXVI) may be prepared by the deprotection of a compound of the formula (XXXVII). Suitable conditions for the deprotection are well known in the art [see, for instance, 'Protecting groups in Organic Synthesis (Second Edition)', Theodora W. Green and Peter G. M. Wuts, John Wiley and Sons, 1991]. In a typical procedure, where P^4 is tetrahydropyran-2-yl, the protecting group may be removed by treating a solution of the compound of the formula (XXXVII) in a suitable solvent, such as ethanol, with an acid such as hydrochloric acid.

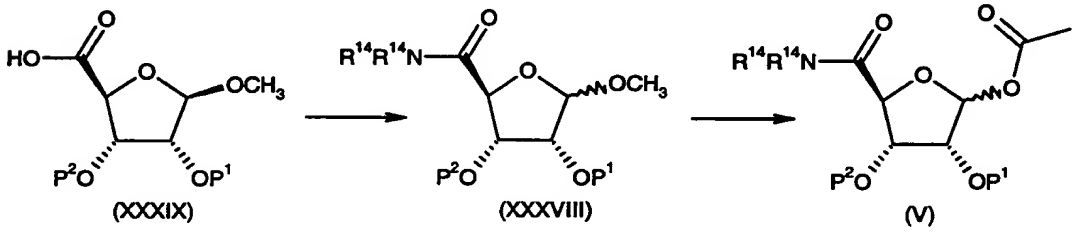
Compounds of the formula (XXXVII) may be prepared by the methanolysis of a compound of the formula (IX). In a typical procedure, a solution of a compound of the formula (IX) in methanol is treated with an alkali metal methoxide, preferably sodium m thoxide, and heated under reflux. The resulting mixture is cooled, evaporated, dissolved in a suitable solvent such as tetrahydrofuran and

treated with an acid, such as hydrochloric acid, preferably 2N hydrochloric acid, to give the compound of the formula (XXXVII).

The skilled man will appreciate that in certain cases, a compound of the formula (XXXIV) may be used directly as a compound of the formula (XXVI) or a compound of the formula (XXXV) may be used directly as a compound of the formula (XXXII), without the intervening deprotecting and protecting steps, if the protecting groups P^1, P^2, and where applicable P^3, are suitable for use in later steps.

Compounds of the formula (V), as used in Schemes 1, 2 and 5, may be prepared as shown in Scheme 6, wherein P^1 and P^2 are as defined above.

Scheme 6



In Scheme 6, compounds of the formula (V) may be prepared by the treatment of a compound of the formula (XXXVIII) with a mixture of acetic acid, acetic anhydride and a strong acid such as hydrochloric or sulphuric acid with cooling (typically to -10 °C). A compound of formula (XXXVIII) may be prepared from an acid of the formula (XXXIX) by activation of the acid as, for example, an acid chloride and treatment of this activated intermediate with a compound of the formula

$R^{14}R^{14}NH$ (XXXX).

In a typical procedure, a compound of formula (XXXIX) is dissolved in a suitable inert solvent (e.g. dichloromethane) and treated with oxalyl chloride and a catalytic amount of N,N-dimethylformamide. After removal of excess solvent and reagent by evaporation under reduced pressure, the residue is dissolved in anhydrous dichloromethane and treated with a compound of the formula (XXXX). With regard to the conditions employed in later steps, it may be appropriate to change the protecting groups P^1 and P^2 in compounds of the formula (XXXVIII). Alternative, suitable protecting groups are well-known to the skilled person [e.g. 'Protecting Groups in Organic Synthesis (Second Edition)', Theodora W. Green and Peter G. M. Wuts, John Wiley and Sons, 1991]. In a typical case, a solution of the compound of formula (XXXVIII) wherein P^1 and P^2 taken together are dimethylmethylene in a suitable solvent such as methanol may treated with an acid such as pyridinium para-toluenesulphonate to give a compound of formula (XXXVIII) wherein P^1 and P^2 are both replaced by H which may be subsequently reprotected with other functionality. For instance, the compound of formula (XXXVIII) wherein P^1 and P^2 are both replaced by H may be dissolved in a suitable solvent such as dichloromethane and the resulting solution may be treated with an acid acceptor, such as pyridine, and benzoyl chloride to give a compound of formula (XXXVIII) wherein P^1 and P^2 are each benzoyl. Compounds of the formula (XXXIX) are known in the art (see, for example, *J. Am. Chem. Soc.*, 1958, **80**, 5168).

Compounds of the formula (XXXX) are either commercially available or easily prepared by methods well known to the person skilled in the art.

Compounds of the formula (VI), as used in Schemes 1, 2 and 5, are either commercially available or easily prepared by methods well known to the person skilled in the art.

A pharmaceutically acceptable salt of a compound of the formula (I) may be readily prepared by mixing together solutions of a compound of the formula (I) and the desired acid or base, as appropriate. The salt may precipitate from

solution and be collected by filtration or may be recovered by evaporation of the solvent.

The anti-inflammatory properties of the compounds of the formula (I) are demonstrated by their ability to inhibit neutrophil function which indicates A2a receptor agonist activity. This was evaluated by determining the compound profile in an assay where superoxide production was measured from neutrophils activated by fMLP. Neutrophils were isolated from human peripheral blood using dextran sedimentation followed by centrifugation through Ficoll-Hypaque solution. Any contaminating erythrocytes in the granulocyte pellet were removed by lysis with ice-cold distilled water. Superoxide production from the neutrophils was induced by fMLP in the presence of a priming concentration of cytochalasin B. Adenosine deaminase was included in the assay to remove any endogenously produced adenosine that might suppress superoxide production. The effect of the compound on the fMLP-induced response was monitored colorometrically from the reduction of cytochrome C within the assay buffer. The potency of the compounds was assessed by the concentration giving 50% inhibition (IC_{50}) compared to the control response to fMLP.

The compounds of the formula (I) can be administered alone but will generally be administered in admixture with a suitable pharmaceutical excipient, diluent or carrier selected with regard to the intended route of administration and standard pharmaceutical practice.

For example, the compounds of the formula (I) can be administered orally, buccally or sublingually in the form of tablets, capsules, ovules, elixirs, solutions or suspensions, which may contain flavouring or colouring agents, for immediate-, delayed-, sustained-, pulsed- or controlled-release applications.

Such tablets may contain excipients such as microcrystalline cellulose, lactose, sodium citrate, calcium carbonate, dibasic calcium phosphate and glycine, disintegrants such as starch (preferably corn, potato or tapioca starch), sodium

starch glycollate, croscarmellose sodium and certain complex silicates, and granulation binders such as polyvinylpyrrolidone, hydroxypropylmethylcellulose (HPMC), hydroxypropylcellulose (HPC), sucrose, gelatin and acacia. Additionally, lubricating agents such as magnesium stearate, stearic acid, glyceryl behenate and talc may be included.

Solid compositions of a similar type may also be employed as fillers in gelatin capsules. Preferred excipients in this regard include lactose, starch, a cellulose, milk sugar or a high molecular weight polyethylene glycol. For aqueous suspensions and/or elixirs, the compounds of the formula (I) may be combined with various sweetening or flavouring agents, colouring matter or dyes, with emulsifying and/or suspending agents and with diluents such as water, ethanol, propylene glycol or glycerin, and combinations thereof.

The compounds of the formula (I) can also be administered parenterally, for example, intravenously, intra-arterially, intraperitoneally, intrathecally, intraventricularly, intrasternally, intracranially, intramuscularly or subcutaneously, or they may be administered by infusion techniques. They are best used in the form of a sterile aqueous solution which may contain other substances, for example, enough salts or glucose to make the solution isotonic with blood. The aqueous solutions should be suitably buffered (preferably to a pH of from 3 to 9), if necessary. The preparation of suitable parenteral formulations under sterile conditions is readily accomplished by standard pharmaceutical techniques well-known to those skilled in the art.

For oral and parenteral administration to human patients, the daily dosage level of the compounds of the formula (I) will usually be from 0.01 to 100 mg/kg, preferably from 0.1 to 100 mg/kg (in single or divided doses).

Thus tablets or capsules of the compound of the formula (I) may contain from 5 to 500 mg of active compound for administration singly or two or more at a time, as appropriate. The physician in any event will determine the actual

dosage which will be most suitable for any individual patient and it will vary with the age, weight and response of the particular patient. The above dosages are exemplary of the average case. There can, of course, be individual instances where higher or lower dosage ranges are merited and such are within the scope of this invention.

The compounds of formula (I) can also be administered intranasally or by inhalation and are conveniently delivered in the form of a dry powder inhaler or an aerosol spray presentation from a pressurised container, pump, spray, atomiser or nebuliser, with or without the use of a suitable propellant, e.g. dichlorodifluoromethane, trichlorofluoromethane, dichlorotetrafluoroethane, a hydrofluoroalkane such as 1,1,1,2-tetrafluoroethane (HFA 134A [trade mark]) or 1,1,1,2,3,3,3-heptafluoropropane (HFA 227EA [trade mark]), carbon dioxide or other suitable gas. In the case of a pressurised aerosol, the dosage unit may be determined by providing a valve to deliver a metered amount. The pressurised container, pump, spray, atomiser or nebuliser may contain a solution or suspension of the active compound, e.g. using a mixture of ethanol and the propellant as the solvent, which may additionally contain a lubricant, e.g. sorbitan trioleate. Capsules and cartridges (made, for example, from gelatin) for use in an inhaler or insufflator may be formulated to contain a powder mix of a compound of the formula (I) and a suitable powder base such as lactose or starch.

Aerosol or dry powder formulations are preferably arranged so that each metered dose or "puff" contains from 10 to 4000 µg of a compound of the formula (I) for delivery to the patient. The overall daily dose with an aerosol will be in the range of from 10µg to 20mg which may be administered in a single dose or, more usually, in divided doses throughout the day.

Alternatively, the compounds of the formula (I) can be administered in the form of a suppository or pessary, or they may be applied topically in the form of a lotion, solution, cream, ointment or dusting powder. The compounds of the

formula (I) may also be transdermally administered, for example, by the use of a skin patch.

For application topically to the skin, the compounds of the formula (I) can be formulated as a suitable ointment containing the active compound suspended or dissolved in, for example, a mixture with one or more of the following: mineral oil, liquid petrolatum, white petrolatum, propylene glycol, polyoxyethylene polyoxypropylene compound, emulsifying wax and water. Alternatively, they can be formulated as a suitable lotion or cream, suspended or dissolved in, for example, a mixture of one or more of the following: mineral oil, sorbitan monostearate, a polyethylene glycol, liquid paraffin, polysorbate 60, cetyl esters wax, cetearyl alcohol, 2-octyldodecanol, benzyl alcohol and water.

The compounds of the formula (I) may also be used in combination with a cyclodextrin. Cyclodextrins are known to form inclusion and non-inclusion complexes with drug molecules. Formation of a drug-cyclodextrin complex may modify the solubility, dissolution rate, bioavailability and/or stability property of a drug molecule. Drug-cyclodextrin complexes are generally useful for most dosage forms and administration routes. As an alternative to direct complexation with the drug the cyclodextrin may be used as an auxiliary additive, e.g. as a carrier, diluent or solubiliser. Alpha-, beta- and gamma-cyclodextrins are most commonly used and suitable examples are described in WO-A-91/11172, WO-A-94/02518 and WO-A-98/55148.

It is to be appreciated that all references herein to treatment include curative, palliative and prophylactic treatment.

Thus the invention provides:

(i) a compound of the formula (I) or a pharmaceutically acceptable salt or solvate thereof;

(ii) a process for the preparation of a compound of the formula (I) or a pharmaceutically acceptable salt or solvate thereof;

(iii) a pharmaceutical composition including a compound of the formula (I) or a pharmaceutically acceptable salt or solvate thereof, together with a pharmaceutically acceptable excipient, diluent or carrier;

(iv) a compound of the formula (I) or a pharmaceutically acceptable salt, solvate or composition thereof, for use as a medicament;

(v) the use of a compound of the formula (I) or of a pharmaceutically acceptable salt, solvate or composition thereof, for the manufacture of a medicament having A2a receptor agonist activity;

(vi) the use of a compound of the formula (I) or of a pharmaceutically acceptable salt, solvate or composition thereof, for the manufacture of an anti-inflammatory agent;

(vii) the use of a compound of the formula (I) or of a pharmaceutically acceptable salt, solvate or composition thereof, for the manufacture of a medicament for the treatment of a respiratory disease;

(viii) use as in (vii) where the disease is selected from the group consisting of adult respiratory distress syndrome (ARDS), bronchitis, chronic bronchitis, chronic obstructive pulmonary disease, cystic fibrosis, asthma, emphysema, bronchiectasis, chronic sinusitis and rhinitis;

(ix) the use of a compound of the formula (I) or of a pharmaceutically acceptable salt, solvate or composition thereof, for the manufacture of a medicament for the treatment of septic shock, male erectile dysfunction, hypertension, stroke, epilepsy, cerebral ischaemia, peripheral vascular disease, post-ischaemic reperfusion injury, diabetes, rheumatoid arthritis, multiple sclerosis, psoriasis, dermatitis, allergic dermatitis, eczema, ulcerative colitis, Crohns disease, inflammatory bowel disease, *Heliobacter pylori* gastritis, non-*Heliobacter pylori* gastritis, non-steroidal anti-inflammatory drug-induced damage to the gastro-intestinal tract or a psychotic disorder, or for wound healing;

(x) a method of treatment of a mammal, including a human being, with a A2a receptor agonist including treating said mammal with an effective

amount of a compound of the formula (I) or with a pharmaceutically acceptable salt, solvate or composition thereof;

(xi) a method of treatment of a mammal, including a human being, to treat an inflammatory disease including treating said mammal with an effective amount of a compound of the formula (I) or with a pharmaceutically acceptable salt, solvate or composition thereof;

(xii) a method of treatment of a mammal, including a human being, to treat a respiratory disease including treating said mammal with an effective amount of a compound of the formula (I) or with a pharmaceutically acceptable salt, solvate or composition thereof;

(xiii) a method as in (xii) where the disease is selected from the group consisting of adult respiratory distress syndrome (ARDS), bronchitis, chronic bronchitis, chronic obstructive pulmonary disease, cystic fibrosis, asthma, emphysema, bronchiectasis, chronic sinusitis and rhinitis;

(xiv) a method of treatment of a mammal, including a human being, to treat septic shock, male erectile dysfunction, hypertension, stroke, epilepsy, cerebral ischaemia, peripheral vascular disease, post-ischaemic reperfusion injury, diabetes, rheumatoid arthritis, multiple sclerosis, psoriasis, dermatitis, allergic dermatitis, eczema, ulcerative colitis, Crohns disease, inflammatory bowel disease, *Heliobacter pylori* gastritis, non-*Heliobacter pylori* gastritis, non-steroidal anti-inflammatory drug-induced damage to the gastro-intestinal tract or a psychotic disorder, or for wound healing, including treating said mammal with an effective amount of a compound of the formula (I) or with a pharmaceutically acceptable salt, solvate or composition thereof; and

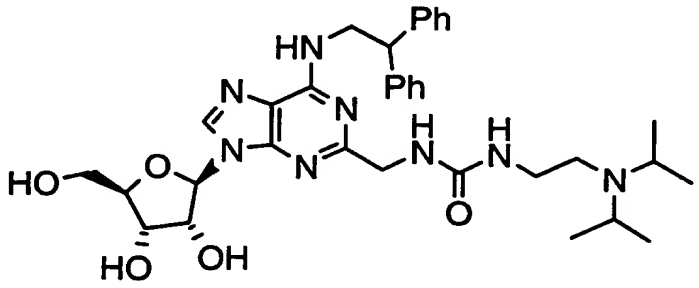
(xv) certain novel intermediates disclosed herein.

The following Examples illustrate the preparation of the compounds of the formula (I).

^{1}H Nuclear magnetic resonance (NMR) spectra were in all cases consistent with the proposed structures. Characteristic chemical shifts (δ) are given in parts-per-million downfield from tetramethylsilane using conventional abbreviations for designation of major peaks: e.g. s, singlet; d, doublet; t, triplet; q, quartet; m, multiplet; br, broad. The mass spectra (m/z) were recorded in either thermospray or electrospray ionisation mode. The following abbreviations have been used for common solvents: $CDCl_3$, deuterochloroform; D_6-DMSO, deuterodimethylsulphoxide; CD_3OD, deuteromethanol. Where thin layer chromatography (TLC) has been used it refers to silica gel TLC using silica gel 60 F_{254} plates, R_f is the distance travelled by a compound divided by the distance travelled by the solvent front on a TLC plate.

Example 1

N-({9-[(2*R*,3*R*,4*S*,5*R*)-3,4-Dihydroxy-5-(hydroxymethyl)tetrahydro-2-furanyl]-6-[(2,2-diphenylethyl)amino]-9*H*-purin-2-yl}methyl)-*N*'-[2-(diisopropylamino)ethyl]urea



N-[2-(Diisopropylamino)ethyl]-1*H*-imidazole-1-carboxamide (84mg, 0.35mmol) (Preparation 3) was added to a stirred solution of (2*R*,3*R*,4*S*,5*R*)-2-{2-(aminomethyl)-6-[(2,2-diphenylethyl)amino]-9*H*-purin-9-yl}-5-(hydroxymethyl)tetrahydro-3,4-furandiol (150mg, 0.35mmol) (Preparation 2) in dichloromethane (5ml) at room temperature. The reaction was heated under

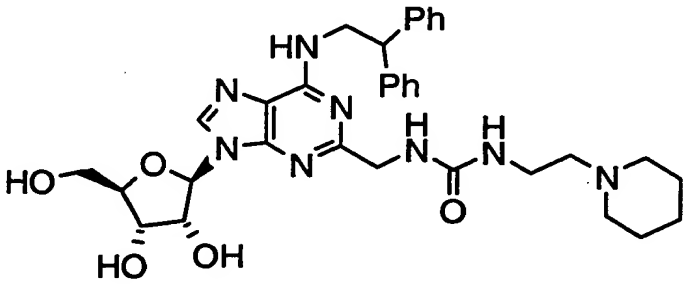
reflux for 1 hour and then toluene (5ml) and isopropanol (2ml) were added. The dichloromethane was boiled off and the reaction was then heated under reflux for 1 hour. The reaction mixture was allowed to cool to room temperature and the solvent was removed under reduced pressure. The residue was purified by column chromatography on silica gel eluting with dichloromethane : methanol : 0.88 concentrated aqueous ammonia (95 : 5 : 0.5 by volume gradually changing to 80 : 20 : 2 by volume) to give the title compound as a foam (60mg).

δ_H (CD_3OD): 8.05 (1H, s), 7.35-7.20 (8H, m), 7.15-7.10 (2H, m), 5.90-5.85 (1H, m), 4.75-4.70 (1H, m), 4.50-4.45 (1H, m), 4.40-4.20 (5H, m), 4.15-4.10 (1H, m), 3.90-3.80 (1H, m), 3.70-3.65 (1H, m), 3.10-3.00 (2H, m), 3.00-2.90 (2H, m), 2.50-2.40 (2H, m), 1.00-0.90 (12H, m).

Analysis: Found C, 61.62; H, 7.12; N, 16.85%; $C_{34}H_{46}N_8O_5.H_2O$ requires C, 61.43; H, 7.28; N, 16.85%.

Example 2

N-({9-[(2*R*,3*R*,4*S*,5*R*)-3,4-Dihydroxy-5-(hydroxymethyl)tetrahydro-2-furanyl]-6-[(2,2-diphenylethyl)amino]-9*H*-purin-2-yl}methyl)-*N'*-[2-(1-piperidinyl)ethyl]urea



A solution of (2*R*,3*R*,4*R*,5*R*)-4-(acetyloxy)-2-[(acetyloxy)methyl]-5-(6-[(2,2-diphenylethyl)amino]-2-{[({[2-(1-piperidinyl)ethyl]amino}carbonyl)amino]methyl}-9*H*-purin-9-yl)tetrahydro-3-furanyl acetate (100mg, 0.13mmol) (Preparation 7) in methanol (50ml) was saturated with ammonia gas and then left to stand for 3 hours. The solvent was removed under reduced pressure to

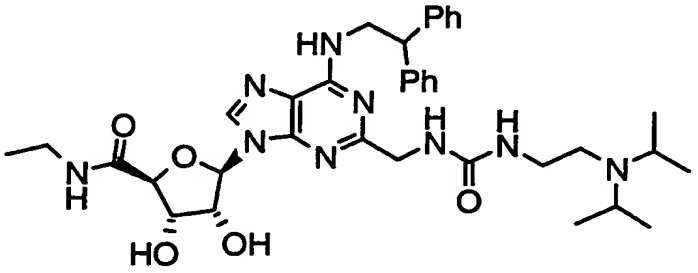
give a residue that was purified by elution through a plug of silica gel with dichloromethane : methanol : 0.88 concentrated aqueous ammonia (90 : 10 : 1 by volume) as the eluant to give the title compound as a foam (45mg).

m/z: MH^+ (631).

δ_H (CD_3OD): 8.15 (1H, s), 7.40-7.15 (10H, m), 6.00-5.90 (1H, m), 4.90-4.70 (signal obscured by HOD in CD_3OD), 4.60-4.10 (7H, m), 3.90-3.80 (1H, m), 3.80-3.70 (1H, m), 3.30-3.20 (2H, m), 2.55-2.35 (6H, m), 1.65-1.40 (6H, m).

Example 3

(2*S*,3*S*,4*R*,5*R*)-5-{2-{[({[2-(Diisopropylamino)ethyl]amino}carbonyl)amino]methyl}-6-[(2,2-diphenylethyl)amino]-9*H*-purin-9-yl}-*N*-ethyl-3,4-dihydroxytetrahydro-2-furancarboxamide



N-[2-(Diisopropylamino)ethyl]-1*H*-imidazole-1-carboxamide (84mg, 0.35mmol) (Preparation 3) was added to a stirred suspension of (2*S*,3*S*,4*R*,5*R*)-5-{2-(aminomethyl)-6-[(2,2-diphenylethyl)amino]-9*H*-purin-9-yl}-*N*-ethyl-3,4-dihydroxytetrahydro-2-furancarboxamide (100mg, 0.23mmol) (Preparation 9) in dichloromethane (5ml) at room temperature. The reaction was then heated to reflux and a drop of isopropanol was added to help solubilise the reagents. The reaction mixture was heated under reflux for 20 minutes and then toluene (5ml) was added. The dichloromethane was boiled off and the reaction was then heated under reflux for 30 minutes. The reaction mixture was allowed to cool to room temperature and the solvent was removed under reduced pressure. The

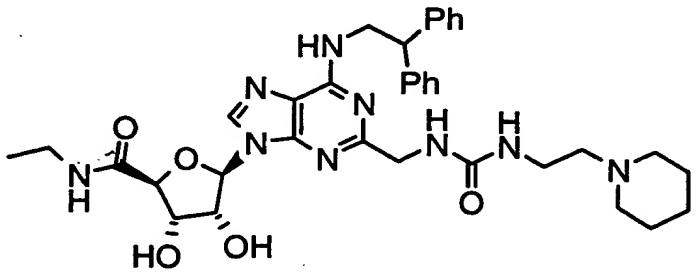
residue was purified by column chromatography on silica gel eluting with dichloromethane : methanol : 0.88 concentrated aqueous ammonia (95 : 5 : 0.5 by volume gradually changing to 80 : 20 : 2 by volume). The solvent was removed under reduced pressure to give a yellow oil. The oil was dissolved in dichloromethane (2ml) and diethylether was added to induce crystallisation. Filtration gave the title compound as a white solid (70mg).

δ_H (CD_3OD): 8.20 (1H, s), 7.40-7.10 (10H, m), 6.10-6.00 (1H, m), 4.90-4.80 (1H obscured by HOD in CD_3OD), 4.55-4.20 (7H, m), 3.40-3.10 (6H, m), 2.75-2.60 (2H, m), 1.20-1.00 (15H, m).

Analysis: Found C, 61.16; H, 7.34; N, 17.63%; $C_{36}H_{49}N_9O_5.H_2O$ requires C, 61.26; H, 7.28; N, 17.86%.

Example 4

(2*S*,3*S*,4*R*,5*R*)-5-(6-[(2,2-Diphenylethyl)amino]-2-{[({[2-(1-piperidinyl)ethyl]amino}carbonyl)amino]methyl}-9*H*-purin-9-yl)-*N*-ethyl-3,4-dihydroxytetrahydro-2-furancarboxamide



Potassium carbonate (20mg, 0.14mmol) was added to a solution of (2*S*,3*S*,4*R*,5*R*)-4-(benzoyloxy)-5-(6-[(2,2-diphenylethyl)amino]-2-{[({[2-(1-piperidinyl)ethyl]amino}carbonyl)amino]methyl}-9*H*-purin-9-yl)-2-[(ethylamino)carbonyl]tetrahydro-3-furanyl benzoate (100mg, 0.13mmol) (Preparation 10) in methanol (10ml). The reaction mixture was stirred at room temperature for 2 hours. More potassium carbonate (20mg, 0.14mmol) was then added and the reaction mixture was heated to 60°C for 2 hours. The

solvent was removed under reduced pressure to give a residue that was slurried with acetone and filtered. The filtrate was evaporated under reduced pressure and the residue was partially purified by column chromatography on silica gel eluting with dichloromethane : methanol : 0.88 concentrated aqueous ammonia (90 : 10 : 1 by volume). Further purification was achieved by column chromatography on silica gel eluting with dichloromethane : methanol : 0.88 concentrated aqueous ammonia (90 : 10 : 1 by volume). The solvent was removed by evaporation under reduced pressure to give the title compound as a foam (17mg).

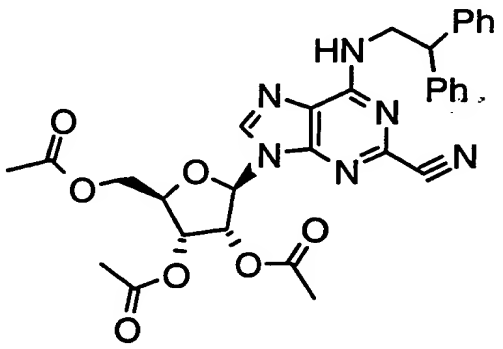
m/z: MH^+ (673).

δ_H (CD_3OD): 8.20 (1H, s), 7.40-7.15 (10H, m), 6.05-6.00 (1H, m), 4.90-4.80 (1H obscured by HOD in MeOH), 4.55-4.20 (7H, m), 3.40-3.20 (4H, m), 2.55-2.40 (6H, m), 1.70-1.50 (4H, m), 1.50-1.40 (2H, m), 1.15-1.05 (3H, m).

The following Preparations describe the preparation of certain intermediates used in the preceding Examples.

Preparation 1

(2*R*,3*R*,4*R*,5*R*)-4-(Acetyloxy)-2-[(acetyloxy)methyl]-5-{2-cyano-6-[(2,2-diphenylethyl)amino]-9*H*-purin-9-yl}tetrahydro-3-furanyl acetate



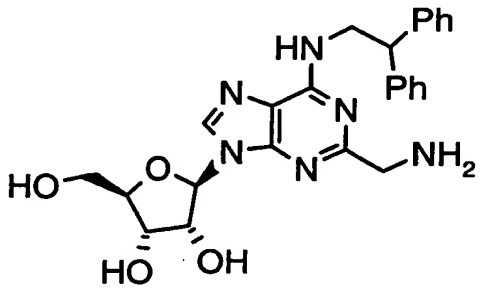
N,O-Bistrimethylsilylacetamide (44ml, 0.18mol) was added to a suspension of 6-[(2,2-diphenylethyl)amino]-9*H*-purine-2-carbonitrile (10.0g, 0.03mol) (see WO-A-00/23457) in 1,1,1-trichloroethane (250ml). The suspension was heated to reflux. When all suspended solid had dissolved the reaction mixture was allowed to cool to room temperature and the solvent was removed under reduced pressure. The residue was twice dissolved in toluene (50ml) and the solvent removed under reduced pressure. The residue was then dissolved in toluene (100ml) and (2*R*,3*R*,4*R*,5*S*)-4,5-bis(acetyloxy)-2-[(acetyloxy)methyl]tetrahydro-3-furanyl acetate (10.3g, 0.032mol) was added. The solution was stirred at room temperature and trimethylsilyltrifluoromethanesulphonate (16ml, 0.088mol) was carefully added. The resulting solution was heated under reflux for 2 hours and then allowed to cool to room temperature. The reaction mixture was diluted by the addition of ethyl acetate (100ml) and then washed with saturated aqueous sodium hydrogen carbonate (ten portions of 100ml) and saturated aqueous sodium chloride solution (100ml). The aqueous extracts were combined and washed with ethyl acetate (three portions of 100ml). The combined organic layers were

dried (anhydrous magnesium sulphate) and the solvent was removed under reduced pressure to give a solid that was purified by column chromatography on silica gel eluting with dichloromethane : methanol : 0.88 concentrated aqueous ammonia (97 : 3 : 0.5 by volume gradually changing to 80 : 20 : 3 by volume) to give the title compound as a foam (8.5g).

δ_H ($CDCl_3$): 7.95 (1H, s), 7.35-7.20 (10H, m), 6.15-6.10 (1H, m), 5.95-5.90 (1H, m), 5.80-5.75 (1H, m), 5.60-5.55 (1H, m), 4.45-4.35 (4H, m), 4.35-4.25 (2H, m), 2.15 (3H, s), 2.10 (3H, s), 2.05 (3H, s).

Preparation 2

(2*R*,3*R*,4*S*,5*R*)-2-{2-(Aminomethyl)-6-[(2,2-diphenylethyl)amino]-9*H*-purin-9-yl}-5-(hydroxymethyl)tetrahydro-3,4-furandiol



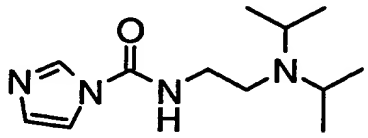
10% w/w Palladium on carbon (200mg) was added to a solution of (2*R*,3*R*,4*R*,5*R*)-4-(acetyloxy)-2-[(acetyloxy)methyl]-5-{2-cyano-6-[(2,2-diphenylethyl)amino]-9*H*-purin-9-yl}tetrahydro-3-furanyl acetate (Preparation 1) (1.9g, 3.2mmol) in ethanol saturated with ammonia (100ml). The reaction mixture was stirred under an atmosphere of hydrogen 414kPa (60psi) for 16 hours at room temperature. The solids were removed by filtration through Arbocel (Trade Mark) and the solvent was removed under reduced pressure. The residue was purified by column chromatography on silica gel eluting with dichloromethane : methanol : 0.88 concentrated aqueous ammonia (90 : 10 : 1 by volume gradually changing to 80 : 20 : 2 by volume) to give the title compound as a solid (770mg).

m/z: MH^+ (477).

δ_H ($CDCl_3$): 8.10 (1H, s), 7.35-7.20 (8H, m), 5.90-5.85 (1H, m), 4.75-4.70 (1H, m), 4.50-4.40 (1H, m), 4.30-4.20 (2H, m), 4.10 (1H, m), 3.90-3.80 (2H, m), 3.70-3.65 (1H, m).

Preparation 3

N-[2-(Diisopropylamino)ethyl]-1*H*-imidazole-1-carboxamide

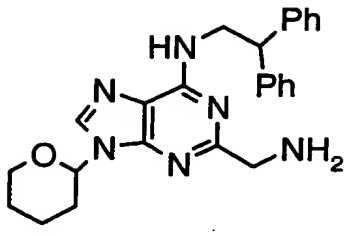


N^1,N^1-Diisopropyl-1,2-ethanediamine (1g, 6.94 mmol) was added to a stirred solution of 1,1'-carbonyldiimidazole (1.12g, 6.94mmol) in dichloromethane (50ml) at room temperature. The reaction mixture was stirred for 1 hour and then diluted with more dichloromethane (50ml), washed with water (60ml), dried (anhydrous magnesium sulphate) and evaporated under reduced pressure to give the title compound as a solid (600mg).

δ_H ($CDCl_3$): 8.05 (1H, s), 7.25 (1H, s), 7.05 (1H, s), 6.65 (1H, br s), 3.40-3.35 (2H, m), 3.10-3.00 (2H, m), 2.75-2.70 (2H, m), 1.05-1.00 (6H, m).

Preparation 4

2-(Aminomethyl)-*N*-(2,2-diphenylethyl)-9-tetrahydro-2*H*-pyran-2-yl-9*H*-purin-6-amine

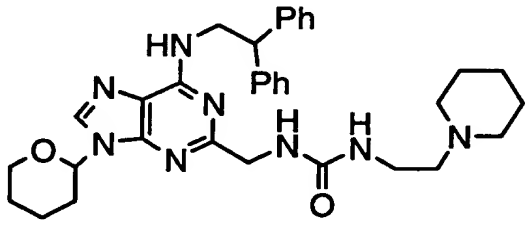


6-[(2,2-Diphenylethyl)amino]-9-tetrahydro-2*H*-pyran-2-yl-9*H*-purine-2-carbonitrile (19.7g, 0.046mol) (see WO-A-00/23457) was dissolved in a saturated solution of ammonia in ethanol (500ml). 10% w/w Palladium on Carbon (2g) was added and the suspension was stirred under an atmosphere of hydrogen (414kPa, 60psi) for 36 hours. The suspension was filtered through Arbocel (Trade Mark) and the solvent was removed under reduced pressure to give the title compound as a foam (17.7g).

δ_H ($CDCl_3$): 7.84 (1H, s), 7.36-7.14 (10H, m), 5.70 (1H, d), 5.60 (1H, br s), 4.42-4.20 (3H, m), 4.14 (1H, d), 3.95 (2H, s), 3.78 (1H, t), 2.20-1.90 (5H, m), 1.88-1.50 (3H, m).

Preparation 5

N-({6-[(2,2-Diphenylethyl)amino]-9-tetrahydro-2*H*-pyran-2-yl-9*H*-purin-2-yl}methyl)-*N'*-[2-(1-piperidinyl)ethyl]urea



2-(1-Piperidinyl)ethanamine (0.35ml, 2.46mmol) was added to a solution of 1,1'-carbonyldiimidazole (420mg, 2.6mmol) in dichloromethane (100ml). The reaction mixture was stirred for ten minutes at room temperature and then 2-(aminomethyl)-*N*-(2,2-diphenylethyl)-9-tetrahydro-2*H*-pyran-2-yl-9*H*-purin-6-

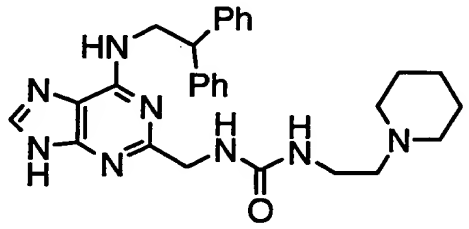
amine (1.0g, 2.33mmol) (Preparation 4) was added. The reaction mixture was stirred for 3 hours at room temperature. Dichloromethane (50ml) was then added and the resulting solution was washed with water (2 x 50ml) and saturated aqueous sodium chloride solution (2 x 50ml). The organic layer was dried (anhydrous magnesium sulphate) and the solvent was removed under reduced pressure. The residue was purified by column chromatography on silica gel eluting with dichloromethane : methanol : 0.88 concentrated aqueous ammonia (93 : 7 : 1 by volume) to give the title compound as an oil (300mg).

m/z: MH^+ (583).

δ_H ($CDCl_3$): 7.85 (1H, s), 7.55 (1H, s), 7.30-7.05 (10H, m), 5.70-5.60 (1H, m), 4.50-4.00 (6H, m), 3.75-3.60 (1H, m), 3.30-3.10 (2H, m), 2.45-2.20 (6H, m), 2.05-1.85 (2H, m), 1.85-1.25 (10H, m).

Preparation 6

N-({6-[(2,2-Diphenylethyl)amino]-9*H*-purin-2-yl}methyl)-*N*'-[2-(1-piperidinyl)ethyl]urea



A solution of *N*-({6-[(2,2-diphenylethyl)amino]-9-tetrahydro-2*H*-pyran-2-yl-9*H*-purin-2-yl}methyl)-*N*'-[2-(1-piperidinyl)ethyl]urea (300mg, 0.51mmol) (Preparation 5) in methanol (150ml) was treated with aqueous hydrochloric acid (2M, 100ml). The reaction mixture was stirred at room temperature for 2 hours. The solvent volume was then reduced to 100ml by evaporation under reduced pressure. Saturated aqueous sodium hydrogen carbonate (50ml) and ethyl acetate (200ml) were added. The two phases were separated. The organic layer was washed with saturated aqueous sodium chloride solution (100ml),

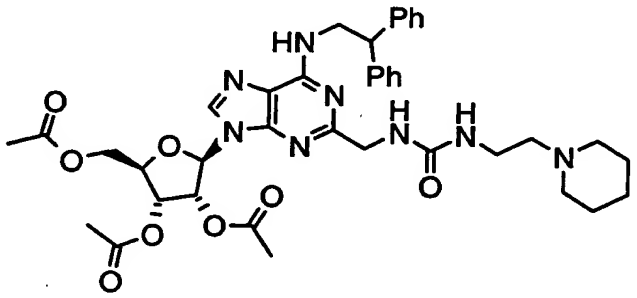
dried (anhydrous magnesium sulphate) and evaporated to give the title compound as a solid (255mg).

m/z: MH^+ (499).

δ_H ($CDCl_3$): 7.80 (1H, s), 7.35-7.10 (10H, m), 4.55-4.10 (5H, m), 3.40-3.20 (2H, m), 2.60-2.30 (6H, m), 1.60-1.25 (6H, m).

Preparation 7

(2*R*,3*R*,4*R*,5*R*)-4-(Acetyloxy)-2-[(acetyloxy)methyl]-5-(6-[(2,2-diphenylethyl)amino]-2-{[({[2-(1-piperidinyl)ethyl]amino}carbonyl)amino]methyl}-9*H*-purin-9-yl)tetrahydro-3-furanyl acetate



N,O-Bistrimethylsilylacetamide (0.34ml, 1.4mmol) was added to a stirred suspension of *N*-({6-[(2,2-diphenylethyl)amino]-9*H*-purin-2-yl}methyl)-*N'*-[2-(1-piperidinyl)ethyl]urea (100mg, 0.2mmol) (Preparation 6) in 1,1,1-trichloroethane (20ml) at 50°C. The reaction mixture was stirred at this temperature for 30 minutes, allowed to cool to room temperature and then evaporated under reduced pressure. Toluene (5ml) was added and the solvent was removed under reduced pressure. The residue was redissolved in toluene (20ml) and (2*R*,3*R*,4*R*,5*S*)-4,5-bis(acetyloxy)-2-[(acetyloxy)methyl]tetrahydro-3-furanyl acetate (0.064g, 0.2mmol) and then trimethylsilyltrifluoromethanesulphonate (0.1ml, 0.35mmol) were added . The reaction mixture was then heated under reflux for 2 hours. The reaction was allowed to cool to room temperature, diluted with ethyl acetate (100ml), washed with saturated aqueous sodium

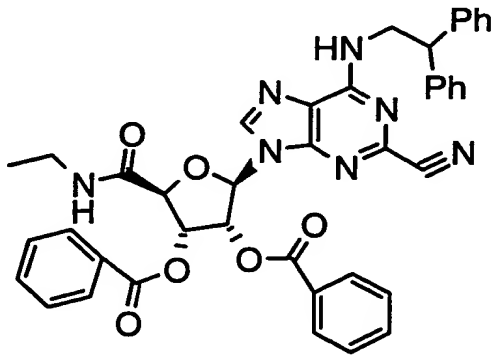
hydrogen carbonate (2 x 50ml) and saturated aqueous sodium chloride solution (50 ml), and then dried (anhydrous magnesium sulphate). The solvent was removed to give a residue that was purified by column chromatography on silica gel eluting with dichloromethane : methanol : 0.88 concentrated aqueous ammonia (90 : 10 : 1 by volume) to give the title compound as an oil (100mg).

m/z: MH^+ (757).

δ_H ($CDCl_3$): 7.65 (1H, s), 7.35-7.15 (10H, m), 6.05-6.00 (1H, m), 6.00-5.90 (2H, m), 5.85-5.75 (1H, m), 5.45-5.40 (1H, m), 4.60-4.15 (7H, m), 3.35-3.25 (2H, m), 2.50-2.35 (6H, m), 2.15 (3H, s), 2.10 (3H, s), 1.90 (3H, s), 1.60-1.35 (6H, m).

Preparation 8

(2*S*,3*S*,4*R*,5*R*)-4-(Benzoyloxy)-5-{2-cyano-6-[(2,2-diphenylethyl)amino]-9*H*-purin-9-yl}-2-[(ethylamino)carbonyl]tetrahydro-3-furanyl benzoate



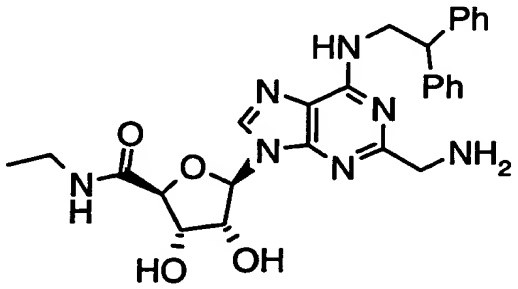
A mixture of 6-[(2,2-diphenylethyl)amino]-9*H*-purine-2-carbonitrile (see WO-A-00/23457) (5.00g, 14.7mmol), (2*S*,3*S*,4*R*,5*R*)-5-(acetyloxy)-4-(benzoyloxy)-2-[(ethylamino)carbonyl]tetrahydro-3-furanyl benzoate and (2*S*,3*S*,4*R*,5*S*)-5-(acetyloxy)-4-(benzoyloxy)-2-[(ethylamino)carbonyl]tetrahydro-3-furanyl benzoate (Preparation 14) (6.50g, 14.7mmol) and iodine (0.38g, 15.0mmol) were heated together at 150°C under reduced pressure (7kPa, 1psi) for 2.5 hours. The reaction was then allowed to stand at room temperature for 18 hours. The residue was purified by column chromatography on silica gel eluting

with a gradient system of ethyl acetate : pentane (40 : 60 by volume) increasing in polarity to neat ethyl acetate to afford the title compound as a foam (4.95g).

δ_H ($CDCl_3$): 8.20-8.00 (3H, m), 7.85-7.75 (2H, m), 7.75-7.65 (2H, m), 7.65-7.45 (3H, m), 7.38-7.16 (11H, m), 6.40-6.30 (1H, m), 6.15-5.95 (3H, m), 4.94 (1H, m), 4.40-4.25 (3H, m), 3.70-3.45 (2H, m), 1.30 (3H, t).

Preparation 9

(2*S*,3*S*,4*R*,5*R*)-5-{2-(Aminomethyl)-6-[(2,2-diphenylethyl)amino]-9*H*-purin-9-yl}-*N*-ethyl-3,4-dihydroxytetrahydro-2-furancarboxamide hydrochloride



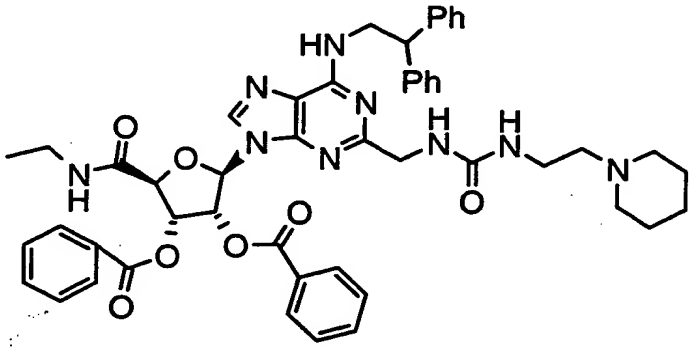
10% w/w Palladium on carbon (400mg) was added to a solution of (2*S*,3*R*,4*R*,5*R*)-4-(benzoyloxy)-5-{2-cyano-6-[(2,2-diphenylethyl)amino]-9*H*-purin-9-yl}-2-[(ethylamino)carbonyl]tetrahydro-3-furanyl benzoate (Preparation 8) (2.0g, 2.70mmol) in ethanol saturated with ammonia (40ml). The reaction mixture was stirred under an atmosphere of hydrogen (414kPa, 60psi) for 16 hours at room temperature, filtered through Arbocel (Trade Mark) and evaporated under reduced pressure. The residue was purified by column chromatography on silica gel eluting with dichloromethane : methanol : 0.88 concentrated aqueous ammonia (95 : 5 : 0.5 by volume gradually changing to 90 : 10 : 1 by volume) to give the title compound as a solid (1.2g).

δ_H (D_6-DMSO): 8.55 (1H, s), 8.45-8.30 (1H, br s), 7.45-7.10 (10H, m), 6.10-6.00 (1H, m), 4.70-4.50 (2H, m), 4.35-4.10 (6H, m), 3.20-3.05 (2H, m), 1.10-0.95 (3H, m).

Analysis: Found C, 53.51; H, 5.75; N, 15.94%. $C_{27}H_{31}N_7O_4.HCl.2H_2O$ requires C, 53.28; H, 5.80; N, 16.11%.

Preparation 10

(2*S*,3*S*,4*R*,5*R*)-4-(Benzoyloxy)-5-(6-[(2,2-diphenylethyl)amino]-2-{[({[2-(1-piperidinyl)ethyl]amino}carbonyl)amino]methyl}-9*H*-purin-9-yl)-2-[(ethylamino)carbonyl]tetrahydro-3-furanyl benzoate

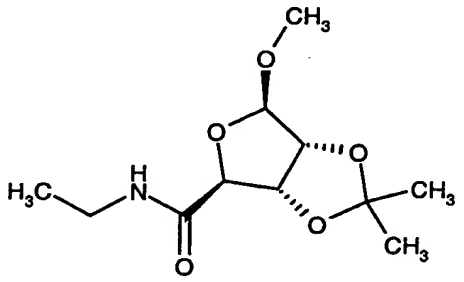


N,O-Bistrimethylsilylacetamide (0.34ml, 1.4mmol) was added to a stirred suspension of *N*-({6-[(2,2-diphenylethyl)amino]-9*H*-purin-2-yl}methyl)-*N'*-[2-(1-piperidinyl)ethyl]urea (100mg, 0.2mmol) (Preparation 6) in 1,1,1-trichloroethane (20ml) at 50°C. The reaction mixture was stirred at this temperature for 30 minutes, allowed to cool to room temperature and then evaporated under reduced pressure. Toluene (5ml) was added and the solvent was removed under reduced pressure. The residue was redissolved in toluene (20ml). (2*S*,3*S*,4*R*,5*R*)-5-(Acetyloxy)-4-(benzoyloxy)-2-[(ethylamino)carbonyl]tetrahydro-3-furanyl benzoate and (2*S*,3*S*,4*R*,5*S*)-5-(acetyloxy)-4-(benzoyloxy)-2-[(ethylamino)carbonyl]tetrahydro-3-furanyl benzoate (90mg, 0.2mmol) (Preparation 14) and then trimethylsilyltrifluoromethanesulphonate (0.1ml, 0.35mmol) were added and the reaction mixture was heated under reflux for 2 hours. The reaction was then allowed to cool to room temperature, diluted with ethyl acetate (100ml), washed with saturated aqueous sodium hydrogen carbonate (2 x 50ml) and saturated aqueous sodium chloride solution (50 ml)

and then dried (anhydrous magnesium sulphate). The solvent was removed to give a residue that was purified by column chromatography on silica gel eluting with dichloromethane : methanol : 0.88 concentrated aqueous ammonia (95 : 5 : 0.5 by volume) to give an impure oil (100mg) which was used without further purification in subsequent experiments.

Preparation 11

(3a*S*,4*S*,6*R*,6a*R*)-*N*-Ethyl-6-methoxy-2,2-dimethyltetrahydrofuro[3,4-*d*][1,3]dioxole-4-carboxamide



Oxalyl chloride (14.0 ml, 160 mmol) was added dropwise to a stirred solution of (3a*R*,4*S*,6*R*,6a*R*)-6-methoxy-2,2-dimethyltetrahydrofuro[3,4-*d*][1,3]dioxole-4-carboxylic acid (*J. Am. Chem. Soc.*, 1958, **80**, 5168) (23.30 g, 107 mmol) in a mixture of anhydrous dichloromethane (120 ml) and N,N'-dimethylformamide (2 drops) and the mixture was stirred at room temperature for 3 hours until gas evolution had ceased. TLC analysis showed that some starting material still remained and therefore more N,N-dimethylformamide (2 drops) was added and stirring was continued for 1 hour. The solvent was removed under reduced pressure and the residue was azeotroped twice with anhydrous dichloromethane (2 x 60 ml). The residue was then dissolved in anhydrous dichloromethane (200 ml) and treated dropwise with a solution of ethylamine in tetrahydrofuran (2M, 140 ml, 280 mmol). The resulting solution was left to stand at room temperature for 48 hours. Diethyl ether (250 ml) was added and the mixture was stirred for 15 minutes, filtered and evaporated under reduced pressure. The residue was purified by column chromatography on silica gel eluting with a gradient system of dichloromethane : ethyl acetate (100 : 0 by

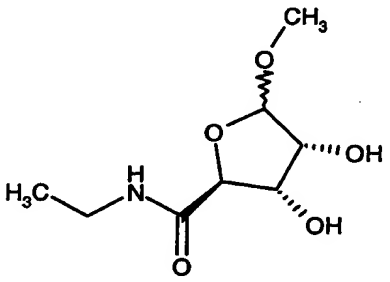
volume) gradually changing to dichloromethane : ethyl acetate (44 : 66 by volume) to afford the title compound as a yellow solid (24.70 g).

m/z: [MH^+] 246.

δ_H ($CDCl_3$): 6.53 (1H, br s), 5.12 (1H, dd), 5.07 (1H, d), 4.60 (1H, d), 4.54 (1H, dd), 3.46 (3H, s), 3.40-3.20 (2H, m), 1.51 (3H, s), 1.34 (3H, s), 1.15 (3H, t).

Preparation 12

(2*S*,3*S*,4*R*,5*R*)-*N*-Ethyl-3,4-dihydroxy-5-methoxytetrahydro-2-furancarboxamide and (2*S*,3*S*,4*R*,5*S*)-*N*-ethyl-3,4-dihydroxy-5-methoxytetrahydro-2-furancarboxamide

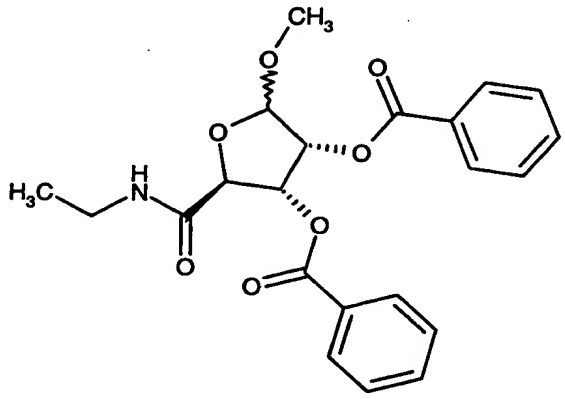


A solution of (3a*R*,4*S*,6*R*,6a*R*)-*N*-ethyl-6-methoxy-2,2-dimethyltetrahydrofuro[3,4-*d*][1,3]dioxole-4-carboxamide (Preparation 11) (24.60 g, 100 mmol) and pyridinium *p*-toluenesulphonate (2.50 g, 10 mmol) in methanol (500 ml) was heated under reflux for 18 hours. NMR analysis showed that some starting material still remained. The solvent was removed under reduced pressure and a solution of the residue in methanol (500 ml) was heated under reflux for 8 hours. NMR analysis showed that some starting material still remained therefore the solvent was removed under reduced pressure once more and a solution of the residue in methanol (500 ml) was heated under reflux for a further 24 hours. The solvent was then removed under reduced pressure and the residue was azeotroped three times with dichloromethane to afford the title compound as an oil and as a mixture of α and β anomers (20.50 g).

δ_H ($CDCl_3$): 6.58 (1H, br m), 4.99 (0.25H, d), 4.94 (0.75H, d), 4.46 (0.25H, d), 4.37 (1.5H, m), 4.24 (0.25H, dd), 4.05 (1H, m), 3.52 (0.75H, s), 3.47 (2.25H, s), 3.30 (2H, m), 1.16 (3H, m).

Preparation 13

(2*S*,3*S*,4*R*,5*R*)-4-(Benzoyloxy)-2-[(ethylamino)carbonyl]-5-methoxytetrahydro-3-furanyl benzoate and (2*S*,3*S*,4*R*,5*S*)-4-(benzoyloxy)-2-[(ethylamino)carbonyl]-5-methoxytetrahydro-3-furanyl benzoate



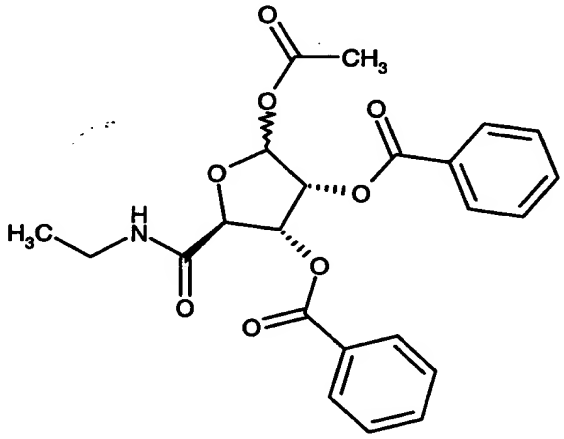
A solution of benzoyl chloride (30.0 ml, 259 mmol) in dichloromethane (100 ml) was added slowly to a solution of (2*S*,3*S*,4*R*,5*R*)-*N*-ethyl-3,4-dihydroxy-5-methoxytetrahydro-2-furancarboxamide and (2*S*,3*S*,4*R*,5*S*)-*N*-ethyl-3,4-dihydroxy-5-methoxytetrahydro-2-furancarboxamide (Preparation 12) (20.50 g, 100 mmol) and pyridine (33.0 ml, 409 mmol) in dichloromethane (400 ml) and the resulting mixture was stirred at room temperature for 18 hours. The solvent was removed under reduced pressure and the residue was partitioned between diethyl ether and aqueous hydrochloric acid (1M, 300 ml). The layers were separated and the aqueous layer was re-extracted with diethyl ether. The organic layers were combined, washed sequentially with water and brine, dried over anhydrous magnesium sulphate, filtered and evaporated under reduced pressure. The residue was purified by column chromatography on silica gel eluting with a gradient system of dichloromethane : diethyl ether

(95 : 5 by volume) gradually changing to dichloromethane : diethyl ether (80 : 20 by volume) to afford the title compound as an oil and as a mixture of α and β anomers (37.0 g).

δ_H ($CDCl_3$): 8.16 (0.5H, d), 7.95 (1.5H, d), 7.88 (1.5H, d), 7.81 (0.5H, d), 7.60-7.25 (6H, m), 6.70-6.60 (1H, br m), 5.90-5.85 (1H, m), 5.60 (0.75H, dd), 5.46 (0.25H, d), 5.23 (0.75H, d), 5.17 (0.25H, t), 4.85-4.75 (1H, m), 3.59 (2.25H, s), 3.49 (0.75H, s), 3.45-3.30 (2H, m), 1.23 (3H, t).

Preparation 14

(2*S*,3*S*,4*R*,5*R*)-5-(Acetyloxy)-4-(benzoyloxy)-2-[(ethylamino)carbonyl]tetrahydro-3-furanyl benzoate and (2*S*,3*S*,4*R*,5*S*)-5-(acetyloxy)-4-(benzoyloxy)-2-[(ethylamino)carbonyl]tetrahydro-3-furanyl benzoate



A solution of (2*S*,3*S*,4*R*,5*R*)-4-(benzoyloxy)-2-[(ethylamino)carbonyl]-5-methoxytetrahydro-3-furanyl benzoate and (2*S*,3*S*,4*R*,5*S*)-4-(benzoyloxy)-2-[(ethylamino)carbonyl]-5-methoxytetrahydro-3-furanyl benzoate (Preparation 13) (37.0 g, 89.6 mmol) in a mixture of acetic acid (330 ml, 5.77 mol) and acetic anhydride (67 ml, 709 mmol) was cooled to -10°C and treated dropwise with aqueous hydrochloric acid (12M, 7.0 ml, 132 mmol). The mixture was stirred for 18 hours, during which time it was allowed to warm to room temperature. After cooling to 0°C, the mixture was diluted slowly with water (1000 ml) and then extracted three times with ethyl acetate (3 portions of 500 ml). The organic layers were combined, washed sequentially with water, a saturated aqueous

solution of sodium hydrogen carbonate and brine, dried over anhydrous magnesium sulphate, filtered and evaporated under reduced pressure. The residue was purified by column chromatography on silica gel eluting with a gradient system of diethyl ether : pentane (66 : 44 by volume) gradually changing to diethyl ether : pentane (100 : 0 by volume). The residue was further purified by column chromatography on silica gel eluting with a gradient system of dichloromethane : diethyl ether (95 : 5 by volume) gradually changing to dichloromethane : diethyl ether (90 : 10 by volume) to afford the title compound as a mixture of α- and β-anomers (15.40 g).

δ_H ($CDCl_3$): 8.12 (0.8H, d), 7.97 (1.2H, d), 7.92 (1.2H, d), 7.79 (0.8H, d), 7.65-7.25 (6H, m), 6.73 (0.4H, d), 6.62 (0.4H, br m), 6.46 (0.6H, br m), 6.42 (0.6H, d), 6.07 (0.4H, dd), 5.95 (0.6H, t), 5.72 (0.6H, d), 5.44 (0.4H, t), 4.94 (0.4H, d), 4.86 (0.6H, d), 3.36 (2H, m), 2.17 (1.8H, s), 2.10 (1.2H, s), 1.20 (3H, m).

It will be appreciated that what will be claimed is as follows:

(i) a compound of the formula (I) or a pharmaceutically acceptable salt or solvate thereof;

(ii) a process for the preparation of a compound of the formula (I) or a pharmaceutically acceptable salt or solvate thereof;

(iii) a pharmaceutical composition including a compound of the formula (I) or a pharmaceutically acceptable salt or solvate thereof, together with a pharmaceutically acceptable excipient, diluent or carrier;

(iv) a compound of the formula (I) or a pharmaceutically acceptable salt, solvate or composition thereof, for use as a medicament;

(v) the use of a compound of the formula (I) or of a pharmaceutically acceptable salt, solvate or composition thereof, for the manufacture of a medicament having A2a receptor agonist activity;

(vi) the use of a compound of the formula (I) or of a pharmaceutically acceptable salt, solvate or composition thereof, for the manufacture of an anti-inflammatory agent;

(vii) the use of a compound of the formula (I) or of a pharmaceutically acceptable salt, solvate or composition thereof, for the manufacture of a medicament for the treatment of a respiratory disease;

(viii) use as in (vii) where the disease is selected from the group consisting of adult respiratory distress syndrome (ARDS), bronchitis, chronic bronchitis, chronic obstructive pulmonary disease, cystic fibrosis, asthma, emphysema, bronchiectasis, chronic sinusitis and rhinitis;

(ix) the use of a compound of the formula (I) or of a pharmaceutically acceptable salt, solvate or composition thereof, for the manufacture of a medicament for the treatment of septic shock, male erectile dysfunction, hypertension, stroke, epilepsy, cerebral ischaemia, peripheral vascular disease, post-ischaemic reperfusion injury, diabetes, rheumatoid arthritis, multiple sclerosis, psoriasis, dermatitis, allergic dermatitis, eczema, ulcerative colitis, Crohns disease, inflammatory bowel disease, *Heliobacter pylori* gastritis, non-*Heliobacter pylori* gastritis, non-steroidal

anti-inflammatory drug-induced damage to the gastro-intestinal tract or a psychotic disorder, or for wound healing;

(x) a method of treatment of a mammal, including a human being, with a A2a receptor agonist including treating said mammal with an effective amount of a compound of the formula (I) or with a pharmaceutically acceptable salt, solvate or composition thereof;

(xi) a method of treatment of a mammal, including a human being, to treat an inflammatory disease including treating said mammal with an effective amount of a compound of the formula (I) or with a pharmaceutically acceptable salt, solvate or composition thereof;

(xii) a method of treatment of a mammal, including a human being, to treat a respiratory disease including treating said mammal with an effective amount of a compound of the formula (I) or with a pharmaceutically acceptable salt, solvate or composition thereof;

(xiii) a method as in (xii) where the disease is selected from the group consisting of adult respiratory distress syndrome (ARDS), bronchitis, chronic bronchitis, chronic obstructive pulmonary disease, cystic fibrosis, asthma, emphysema, bronchiectasis, chronic sinusitis and rhinitis;

(xiv) a method of treatment of a mammal, including a human being, to treat septic shock, male erectile dysfunction, hypertension, stroke, epilepsy, cerebral ischaemia, peripheral vascular disease, post-ischaemic reperfusion injury, diabetes, rheumatoid arthritis, multiple sclerosis, psoriasis, dermatitis, allergic dermatitis, eczema, ulcerative colitis, Crohns disease, inflammatory bowel disease, *Heliobacter pylori* gastritis, non-*Heliobacter pylori* gastritis, non-steroidal anti-inflammatory drug-induced damage to the gastro-intestinal tract or a psychotic disorder, or for wound healing, including treating said mammal with an effective amount of a compound of the formula (I) or with a pharmaceutically acceptable salt, solvate or composition thereof; and

(xv) certain novel intermediates disclosed herein.